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PAULA KAREN BRAVERMAN

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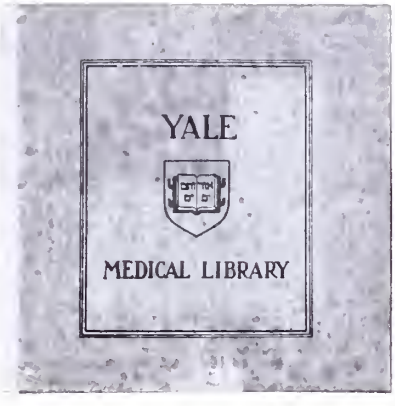
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A CLINICAL TRIAL TO EVALUATE THE COMBINATION OF CLONIDINE AND AN OPIATE ANTAGONIST AS A METHOD OF METHADONE DETOXIFICATION

By Paula Karen Braverman

A thesis submitted to the Yale University School of Medicine

in partial fulfillment of the requirements for the

Degree of Doctor of Medicine

1982

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ACKNOWLEDGEMENTS

I am deeply indebted to Dennis Charney, MD, Herbert Kleber, MD, Charles Riordan, MD, and the staff on the Research Unit at the Connecticut Mental Health Center for their guidance and support in the preparation of this thesis. In addition, I am especially appreciative of the invaluable assistance of Elena DiMassa who typed this manuscript.

ABSTRACT

Recent research developments have found that the long recognized hyperadrenergic state of opiate withdrawal may be mediated by hyperactivity of the locus coeruleus- a nucleus in the anterior pons which is almost entirely composed of norepinephrine. This suggested that clonidine and $\alpha 2$ adrenergic agonist might be effective in inhibiting LC firing and be clinically applicable in attenuating withdrawal symptoms. The current study extends this idea by using an opiate antagonist (naloxone or naltrexone) to precipitate a possibly more intense but shorter lived abstinence syndrome while attempting to minimize withdrawal symptoms with clonidine.

Five men and three women with methadone maintenance doses of 10-35 mg on admission were detoxified on a combination of either clonidine and naloxone or clonidine and naltrexone after abrupt termination of methadone. The clonidine/antagonist protocol proved to be a safe effective method of detoxification without evidence of cardiovascular compromise or uncontrollable severe abstinence symptoms. Most of the withdrawal syndrome was completed within three days of methadone termination while a few mild symptoms persisted for up to one week. A single 50 mg maintenance dose of naltrexone could be administered on the fifth day. Although initial clonidine requirements exceeded those needed in previous studies utilizing clonidine alone, the subjects were able to achieve lower doses and finish the clonidine taper sooner. The most prominent symptoms during detoxification included anxiety, bone and muscle aching, anorexia, insomnia, restlessness, and hot and cold flashes. Suggestions are made for possible application of this method to appropriate methadone maintenance clients.

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INTRODUCTION

HISTORICAL PERSPECTIVE

The use of opiate compounds dates back to at least the third century B.C. when opium was used in many medicinal compounds.[80] Opium eating and smoking became popular in Europe and the Orient and by the 18th century it was apparent that opium use could be associated with dependence. At that time, however, it was believed that the lower classes were most susceptible to its effects and that the upper class showed "no noticeable behavioral changes."[123,p.70] Opium continued to be deemed useful for virtually all ailments and it wasn't until the 19th century that the medical community raised serious questions about the addictive potential of opium for all classes.

By 1868, both oral and intravenous morphine had come into use in the belief that it was safer and preferable to opium in the treatment of disease. During the late 1870's, large amounts of the drug were being imported into the United States. When the addictive potential of morphine became obvious, the general public fear of opiate addiction led to the passage of many antimorphine laws in the 1890's as well as a prohibition on the importation of smoking opium in 1909.[123]

By 1900, there were an estimated 250,000 opiate addicts in the United States.[123] It should be emphasized that physicians were not solely responsible for the opiate problem. Many individuals had become addicted through the use of narcotic containing patent medicines. The first serious

action taken by the federal government to deal with this problem came in 1915 with the passage of the Harrison Narcotic Act. Attempts were made to regulate opiate supplies by registering physicians and pharmacists; placing a limit on the amount of opiate compounds present in patent medicines; and prohibiting addiction maintenance to all individuals unless they had untreatable pain, had become addicted during previous medical care or were elderly debilitated individuals with a long addiction history.[123,124]

Heroin addiction did not become a problem until the late 1910's. Contrary to popular belief, this drug was not introduced as a harmless cure for morphine addiction. Rather, it was initially used as a cough suppressant. It became widely abused by opiate addicts only after restrictive laws were enforced and addicts found it necessary to turn to other sources to support their habits.[97]

The search for a safe effective method of opiate detoxification has been ongoing since the 1800's. Detoxification is defined as "... the process whereby an individual who is physically dependent on the drug ... is taken off that drug ..."[87] This does not imply a cure since the prevention of relapse is not necessarily a goal. Most recently, specific emphasis has been placed on a nonaddicting method of opiate detoxification for the estimated 80,000 individuals on methadone maintenance - 10,000 of whom are attempting withdrawal at any time.[88] These individuals have been knowingly placed on an addictive drug which will prevent the onset of abstinence in an attempt to eliminate the need to seek out an illegal substance (i.e. heroin) while they work on the problems underlying opiate abuse.

Recent clinical trials with the $\alpha 2$ adrenergic agonist clonidine have been promising. However, the protocol requires up to two weeks of clonidine

therapy and does not eliminate the need for a 5-10 day period after methadone is stopped before antagonist aftercare therapy can be begun. The purpose of this study is to evaluate the effectiveness and safety of a clonidine/antagonist combination in methadone detoxification paying specific attention to its ability to shorten both the length of the withdrawal period and the lag time before induction onto maintenance doses of the opiate antagonist naltrexone.

DEFINITIONS

DRUG ADDICTION - As recounted by Isbell, [76] the World Health Organization defined drug addiction as "... a state of periodic or chronic intoxication detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include 1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means. 2) a tendency to increase the dose. 3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug."

Isbell[76] defined more specific aspects of opiate addiction:

TOLERANCE - "...a decreasing effect on repetition of the same dose of a drug."

PHYSICAL DEPENDENCE _ "... the development of an altered physiologic state which requires continued administration of a drug to prevent the appearance of a characteristic illness termed an "abstinence syndrome."

EMOTIONAL DEPENDENCE - "... a substitution of the use of the drug for other types of adaptive behavior."

OPIATE DEPENDENCE AND WITHDRAWAL SYNDROMES

The opiate dependence and withdrawal syndromes have been studied and well documented over the past century. Himmelsbach [63] described the morphine addiction syndrome in detail noting that the morphine addict exhibited evidence of increased appetite, body temperature and ESR; disturbed sleep patterns; lowered respiratory rate, blood pressure, HCT and serum lactic acid levels; as well as normal blood sugar and basal metabolic rate.

Isbell[76] studied the morphine withdrawal syndrome and observed the onset within 12 - 14 hours of abstinence of occasional yawning, mild perspiration, rhinorrhea, and lacrimation. Gooseflesh, muscle twitching, muscle aches, cold flashes and mydriasis were evident at 18-24 hours. Thirty-six hours marked the onset of restlessness, vomiting, diarrhea, anorexia, weight loss and changes in vital signs - i.e. respiratory rate, blood pressure, temperature. These symptoms persisted until 72 hours and subsequently declined in intensity with a return toward baseline in 7 - 10 days. Isbell did note however that individuals complained about insomnia, weakness, nervousness and muscle pain for weeks thereafter.

Kolb[91] made a more detailed study of the morphine abstinence syndrome during the first ten days of withdrawal noting that acute withdrawal was characterized by insomnia; decreased caloric intake and body weight; and elevated blood sugar levels, rectal temperature, respiratory rate, blood pressure, and basal metabolic rate. He found that blood sugar levels returned to pre-withdrawal levels within four days and that caloric intake recovered within six days. The remaining parameters had not returned to baseline within

the ten day study leading him to conclude that withdrawal was not complete in 10 days.

Himmelsbach[63] also believed that the abstinence syndrome lasted longer than 10 days and conducted a longitudinal study in which he observed drug addicts during three time periods - addiction; the first 15 days of withdrawal; and approximately once a month for up to nine months after withdrawal. He found that recovery or the achievement of steady state levels of blood sugar, lactic acid and inorganic phosphate occurred within the first month post-withdrawal while phosphate remained subnormal at nine months. Two to three months were necessary to achieve recovery of body temperature, caloric intake, sleep patterns, and respiratory rate. The discrepancy between Kolb and Himmelsbach with regard to caloric intake can be explained by the length of the observation period. The initial recovery of appetite at one week is followed by a two month period of increased caloric intake over addiction levels. Blood pressure, body weight, basal metabolic rate, hematocrit and erythrocyte sedimentation rate did not stablize for four to six months. As with inorganic phosphate, the basal metabolic rate was felt to be subnormal at nine months.

Martin [111] described this prolonged recovery period in rats and broke it down into primary and secondary or protracted abstinence syndromes. The primary abstinence syndrome began 8-16 hours after abstinence and lasted for 72 hours. It was characterized by weight loss decrease in body temperature, hostile behavior, and wet dog shakes. The protracted abstinence syndrome which included increases in body weight, temperature, BMR, and water consumption lasted up to six months. Martin [115] later went on to study the same phenomenon in humans. The primary abstinence syndrome of elevated blood pressure, temperature, respiratory rate, heart rate, mydriasis, and

increased sensitivity of the respiratory center to CO_2 lasted for approximately two months while the protracted abstinence period characterized by diminished blood pressure, heart rate, and temperature; decreased sensitivity of the respiratory center to CO_2; and miosis became apparent within six to nine weeks after morphine withdrawal and lasted up to 30 weeks. Martin also noted that elevated levels of urine epinephrine could be detected for 17 weeks post withdrawal.

The heroin and methadone abstinence syndromes are slightly different from that of morphine. Heroin is a shorter acting compound with an earlier onset of withdrawal symptoms at 8-12 hours, a shorter peak at 48-72 hours and a faster recovery period of 5-10 days. Methadone has a longer period of action than morphine with a slower onset of withdrawal at 36-72 hours, a later peak at 72-96 hours and a longer recovery period of 14-21 days. Although the methadone withdrawal symptoms are less intense than those of morphine or heroin, weakness, fatigue, aching and insomnia can still be apparent up to six weeks post-withdrawal.[76,87]

Opiate withdrawal symptoms have been graded in an attempt to judge clinical severity.[87] This system is as follows:

Grade 0: Drug craving, anxiety, drug seeking behavior

Grade 1: Yawning, perspiration, lacrimation, rhinorrhea yen sleep

Grade 2: Mydriasis, gooseflesh, muscle twitches, hot and cold flashes, chills, aching bones and muscles, anorexia, irritability

Grade 3: Insomnia, fever, increased respiratory rate and blood pressure, restlessness, abdominal cramps, nausea, vomiting, diarrhea, weakness, weight loss.

It is important to realize that this chart is an approximation. Not all patients will experience the entire spectrum of symptoms, nor will they occur

in this exact order. Patients tend to exhibit a particular set of symptoms which repeat themselves each time that they withdraw.

DETOXIFICATION TECHNIQUES

From the mid 1800's to the 1920's, the medical community believed that opiate addiction was curable. Withdrawal followed by a few weeks of support was considered to be sufficient for attaining this goal.[123] By the late 1800's, the consensus of opinion ran in favor of the use of rapid withdrawal techniques as opposed to slow withdrawal. Although slow withdrawal could be accomplished with minimal symptomatology, rapid methods appeared to be more practical when one considered the tendency of addicts to either change their minds about detoxification or use detoxification for a few weeks as a means of legally procurring opiate compounds.[91] Kolb and Himmelsbach reviewed the major detoxification methods used from 1900-1940. As described below, they proved to be "...useless and even harmful treatments to control or mitigate the severity of the symptoms...".[91]

Belladonna Treatment - This method utilized atropine; scopolamine in addition to strychnine, nitroglycerine and digitalis; or a scopolamine/purgative combination along with oxgall, phenacetin, caffeine, pyramidon, salicytates, sodium nitrate, sodium bromide, sodium bicarbonate, codeine and chloral hydrate. The use of these compounds was based on the theories of eliminating morphine stored in several body tissues including the spinal cord. In addition, intestinal or auto-intoxication was suggested as a cause of toxemia which led to withdrawal symptomatology. Kolb considered these treatments harmful serving only to "knockout" the patients and make them less likely to discontinue treatment.

Peptization and water balance was based on the theory that morphine coagulates protein colloids in the brain and that a peptizing agent i.e. sodium thiocyanate would disperse then while binding water and giving rise to withdrawal symptoms. The recovery of a normal distribution of endogenous peptizing agents signified cure. Kolb pointed out that the use of controls during these trials would have revealed that the patients had suffered more from the sodium thiocyanate, especially in terms of psychotic episodes, than they would have from unassisted morphine withdrawal.

Bromide sleep treatment involved the use of sodium bromide to the point of delerium with subsequent revival using oxygen and strychnine. This method proved to be very dangerous with a death rate of two out ten.

Lipoid Treatments were based on the belief that narcotics extracted lipoids from the nervous system and caused drug craving. Narcosan - a solution of lipoids, nonspecific proteins and water soluble vitamins was used to replace these supposed losses. This treatment was not only dangerous but worsened the patients' withdrawal symptoms.

Endocrine Treatments were attempted when it was noted that thyroid and adrenal function appeared to be altered during withdrawal. Ovarian hormone was even used in the belief that it had a chemical structure resembling morphine. The presence of sympathetic symptoms and hyperglycemia suggested overactivity of the adrenal gland. Sakel[91] and later Tillim [181] used insulin to treat withdrawal symptoms suggesting that it reestablished the equillibrium which was altered by the outpouring of epinephrine as evidenced by hyperglycemia. Kolb suggested that hyperglycemia was not responsible for withdrawal - rather it was a manifestation of increased sympathetic tone. He noted that controlled studies had failed to reveal any affect of insulin on withdrawal.

Finally, immunity treatments were based on the theory that morphine acted as an antigen by initiating an antibody response which poisoned the individual and caused abstinence when morphine was withdrawn. Supposed antibodies were obtained from iatrogenically induced blisters or the patient's own blood (autoheamotherapy) and the fluid was injected either subcutaneously (blister fluid) or intramuscularly (blood). These methods proved to be ineffective although admittedly not as dangerous as those previously discussed methods.

As reviewed by Kleber,[87] since 1940 several other methods of detoxification have been investigated. Convulsive therapy encompasses the use of metrazol,[8] seventy per cent CO_2 inhalation,[8] electric convulsive therapy (ECT)[41,83,180] and nonconvulsive electric shock.[10] Avery[8] claimed that metrazol induced convulsions enabled six out of ten individuals to rapidly decrease their morphine requirements with minimal withdrawal symptoms. ECT was attempted in 1952 by Gallinek.[41] Treatments for seven days produced attenuated withdrawal symptoms with blunting and confusion replacing anxiety and agitation. Thigpen[180] later studied 35 patients and claimed that ECT was "uniformly effective" in eliminating withdrawal symptoms. Furthermore, it enabled the patients to overcome the psychic and emotional aspects of withdrawal. On the basis of one case report in 1964, Kelman[83] agreed with Thigpen concluding the ECT was able to completely suppress the narcotic withdrawal syndrome possibly by causing a temporary frontal lobectomy. He made this statement on the basis of a study by Foltz and White[40] who were able to modify the withdrawal syndrome in monkeys with bilateral cingulumotomy, resection of the cingulate gyri and frontal lobectomy. Foltz suggested that this surgery represented possible disruption of the limbic system and modification of

the autonomic hyperactivity observed in withdrawal. Finally, nonconvulsive electric shock therapy with intravenous barbituates was used by Berkwitz[10] who produced a complete absence of withdrawal symptoms in five subjects after the fifth treatment over a five day period. The lack of controls in his study was a major flaw.

Artificial hibernation was attempted by Newman[126] in 1941. Body temperature was lowered to 88° for two to three days after pretreatment with sodium pentothal and paraldehyde. Withdrawal did occur as evidenced by muscle tremors, restlessness and complaints of muscle pain, diarrhea, abdominal cramps, and nervousness post-hibernation. However, the subjects did not express a desire for opiates. Complications of this method included mesenteric thrombosis and two deaths from circulatory collapse and pneumonia.

The phenothiazine, promazine hydrochloride, was studied by Rolo[152] who found this agent to elicit less drowsiness and fatigue than other phenothiazines. This drug enabled withdrawal to be accomplished without tension, drug craving or other major complications leaving the individual accessible to psychotherapy.

The use of propranolol in drug addiction was reported by Grosz[58] in 1972. He found that this non-narcotic, nonaddicting drug reduced narcotic craving and prevented heroin induced euphoria. However, he felt that it probably was not useful in withdrawal since it seemed to precipitate withdrawal symptoms. Further investigations were performed by Hollister[66] who failed to elicit evidence of antagonist activity and noted that during detoxification smaller doses of methadone were needed when propranolol was used. However, since the most pronounced effects were seen in patients with mild withdrawal symptoms, he also doubted that it would be a useful agent.

Tennant[175] conducted a double blind study to compare the efficacies of propoxyphene napsylate, a mild analgesic with less addictive potential than methadone, to methadone as a method of a 21 day heroin detoxification. Since methadone proved to be more effective in suppressing withdrawal, he felt that the only reason for choosing propxyphene over methadone would be because of its lower abuse and dependence potential.

The use of acupuncture was extensively reviewed by Whitehead[197] who concluded that neither the mechanism of action nor the efficacy of acupuncture for any condition including addiction had been established. Suggestions have been made about the possibility of acupuncture inducing endogenous opiate peptide release[136] (see subsequent discussions). This method requires several treatments for the first few days and daily treatments for up to nine days. Whitehead claimed that the clinical trials had been inadequate because of a lack of controls and an inability to rule out environmental influences.

Methadone has been the most widely used method of treating opiate addiction in the past 15-20 years.[88] It is a synthetic analgesic drug developed in Germany during WWII which exhibited pharmacological properties resembling morphine in animals and man.[74] Isbell[74,75] studied this drug extensively in the late 1940's. Subcutaneously administered methadone could produce euphoria when the dosage exceeded 20 mg and a euphoria of slow onset which lasted up to 48 hours in the 30-60 mg range. Methadone both relieved and prevented morphine abstinence symptoms proving to be cross tolerant to morphine. Furthermore, it was addicting as evidenced by the precipitation of an abstinence syndrome when it was stopped. Tolerance was observed to develop pain threshold elevations, sedative effects, EEG changes, miosis and depressed caloric intake. Individuals on chronic doses showed psychological and

behavioral changes resembling those of morphine addicts and after prolonged use a mild nonprogressive normocytic anemia appeared along with low fasting blood sugars; abnormal dextrose tolerance tests; EEG changes; depressed systolic blood pressure, respiration and pulse; and elevated body temperature.

The abstinence syndrome was described as being mild in comparison to morphine-appearing three days after withdrawal, peaking at six days, and persisting more than two weeks. Symptoms were reported up to 60 days. Isbell claimed that there was less autonomic disturbance especially with respect to vomiting, restlessness, and diarrhea than the morphine abstinence syndrome. However, patients did experience weakness, fatigue, anxiety, abdominal discomfort, anorexia, insomnia; elevated body temperature, systolic blood pressure, and pulse; depressed caloric intake; weight loss and altered glucose tolerance tests. Although this syndrome was less severe than that of morphine abstinence, the persistence of symptoms was bothersome to patients. One person was quoted as saying. "This stuff seems like it never will turn a man loose. When I stop a morphine habit I start getting better on the third day and keep getting better every day after that. I didn't start to get sick until the third day off, and I'm still half sick all the time and not getting better. If I were on the street I'd have shot up within five minutes."[74] Isbell felt that the euphoric properties of this agent and its addictive potential made it "dangerous". He suggested that methadone be substituted for morphine and then tapered off over a 7-10 day period to avoid chronic use.

Martin et al[116] repeated the extensive physiological and psychological studies on orally and subcutaneously administered methadone in 1973. He confirmed most of Isbell's findings and added the information that chronic methadone treatment did not cause any chest x-ray, electrocardiogram or

urinalysis changes. However, nonpathological elevations of SGOT which remained high post-withdrawal were observed as well as decreased levels of LH and FSH. These hormonal changes were used as a partial explanation of complaints of impotence. MMPI studies failed to reveal evidence of psychopathic deviation but the combined results of the MMPI and ARCI scales did show inefficiency, hypochondriasis, lethargy and decreased motivation. He did not agree with Isbell's observations of a paucity of autonomic symptoms. His patients exhibited significant withdrawal symptoms for up to three weeks without complete recovery for six to eight weeks. Furthermore, he suggested that abnormal sleep paterns and unresolved blood pressure, pupillary diameter, and temperature changes which persisted for up to 24 weeks, represented the protracted abstinence syndrome described earlier for morphine.

The use of methadone as a method of heroin detoxification has been studied by several groups. Kleber[87] described a protocol in which methadone substitution is made during the first 24 hours to achieve stabilization. The morphine is then tapered either 5 mg per day or by 5 mg a day until 10-15 mg is reached whereupon small decrements are made as tolerated. By law, the entire procedure cannot exceed 21 days. This issue was addressed by Raynes[138] who felt that 21 days might be inadequate based on an outpatient study in which a mean of 22 days was required for patient controlled methadone detoxification schedules.

Several studies have been conducted to determine the best method of heroin detoxification via methadone. In 1971, Wilson[201] studied a 90 day detoxification in which some participants were only outpatients while the others were outpatients after an initial 7 day inpatient taper to 10 mg. During the outpatient period the group was divided into three sections. Group I took 10

mg of methadone for 30 days, 5 mg for the next 31 days and 2 mg for the remaining period. Group II took 5 mg for 30 days followed by 2 mg for the remainder of the study. Group III received placebo. Only 2 out of 30 subject completed the study while only 4 out of 30 achieved zero dosage. All of the successful clients had returned to narcotic use within one month. Although Group I was more successful than Group III, which did the least well, Wilson concluded that he could find no benefit from low dose methadone protocols or prolonged detoxification techniques. Furthermore, the setting, i.e. inpatient vs. outpatient, did not affect outcome. In discussing this last issue, Kleber[87] felt that the outpatient setting risks temptation but places the patient in the favorable position of seeking help from his usual support systems. Inpatient hospitalization is very expensive and is frequently lacking from sufficient patient-staff interaction or psychiatric intervention. The residential detoxification programs or therapeutic communities do have good staffing but are not ideal for a polydrug abuser. In conclusion, no studies have proven that one method is better than the others.

Stern[172], Razani[139] and Raynes[138] conducted inpatient and outpatient studies which revealed that patient controlled detoxification schedules were more successful than physician-staff controlled protocols. The patients did not abuse the system and in many cases detoxified in a shorter period of time and with lower doses than the standard protocols would have dictated. The significant decrease in staff-patient tension provided a good environment in which to deal with individual social and emotional problems and led to increased self-esteem among the patients. Senay[158] subsequently pointed out that this method might not be good for all addicts. In his experience, some individuals felt less anxious about detoxification when dosing schedules were controlled by a physician.

CAUSES OF ADDICTION AND RELAPSE

By the 1920's, it became apparent that many addicts relapsed after detoxification. Kolb[91] explained this as being due to the "psychic stresses" which caused opiate abuse in the first place and suggested that opiates "produced a seductive calm" which relieved the mental distress. The psychoanalytic view of drug addiction was discussed in detail by Rado[137] and Glover.[42] Essentially "... drug addictions were seen to be psychically determined, artifically induced illnesss; they can exist because drugs exist, and they are brought into being for psychic reasons."[137]

Robins[151] attempted to characterize narcotic abusers in 1967 by studying sociological variables. Her cohort consisted of 235 black males in St. Louis who were born between 1930 and 1934; attended a black elementary school in St. Louis for at least six years; resided in St. Louis between 1959 and 1964; and had a minimum IQ of 85. Fifty-one percent of this group had tried either heroin, marihuana, amphetamines or barbituates. Twelve percent had tried heroin and ten percent were addicted. Over seventy-five percent of heroin abusers had been introduced to the drug between the ages of 16 and 23. She failed to find a relationship between heroin use and occupational status of the guardian or elementary school performance. However, high school drop out rate, delinquency, and absent fathers were common variables in the heroin addicted group.

Valliant[185,186] conducted 12 and 20 year follow ups on a group of 100 narcotic addicts who were admitted to USPHS Hospital in Lexington between August 1952 and January 1953. Prior to that hospitalization, forty-six percent of these individuals had served prison terms. Ninety-six percent had either lost

a parent prior to age 16; had one parent from a different culture; or lived with a female family member after the age of 30. Most had begun abusing drugs in late adolescence and were considered to be antisocial. Ninety-four percent of this group were followed for a minimum of ten years or until the time of death showing a ninety percent relapse rate and a ninety percent rate of imprisonment. Forty-six percent were abstinent at the time of death or last contact and thirty percent had an extend abstinence period of 3-12 years. A nine month prison term followed by a year of parole resulted in a 15 fold greater abstinence rate over individuals who had only had the inpatient experience. Sixty-seven percent of these parolees achieved abstinence for at least one year. At the 20 year followup when most of this cohort were in their 40's, the paroled subjects were still doing better. Of the original group twenty-three percent had died, twenty-five percent were still abusing drugs; up to forty-two percent had achieved stable abstinence; and ten percent were lost to followup. Valliant could not set an arbitrary age for the achievement of abstinence and concluded that employment and nonparental supervision were important for successful rehabilitation.

There are several theories explaining why addicts relapse. The first suggests that addicts have an underlying metabolic disease[34,52] which represents either a preexisting, possibly genetic defect, or a narcotic induced physiological change which creates a "biochemical need".[52] There has been no evidence to date of any genetic defect in narcotic addiction. Certainly, Martin's protracted abstinence syndrome might represent narcotic induced physiological derangements. In addition, opiate receptor or endogenous opiate peptide changes have been proposed (see opiate section for detailed discussion). Goldstein,[52] however, doubts a pure metabolic theory claiming that most

detoxified addicts do not appear to have unrelenting drug craving. He suggests that certain events such as stresses related to employment and family might be important in relapse.

Goldstein tends to agree with the second theory of relapse as proposed by Wikler. In his initial studies with decorticate dogs in 1948, Wikler[198] demonstrated the development of unconditioned tolerance and dependence to opiate compounds. He suggested that such an unconditioned response could be conditioned when unconditioned stimuli were paired with the production of tolerance thus becoming conditioned stimuli which could initiate signs of morphine withdrawal. In later articles[199,200] he expanded this concept stating that unconditioned central contra-adaptive changes develop to the agonist properties of opiate drugs. Concurrent pairing of initially neutral exteroceptive or introceptive stimuli causes them to become conditioned to produce these unconditioned responses even in an abstinent individual. The conditioned stimuli would include drug cult practices,watching others shoot up, or returning to old surroundings associated with drug abuse. Wikler proposed that these responses should be extinguished to prevent relapse (see section on antagonists). In 1977, O'Brien[127] actually was able to produce conditioned narcotic withdrawal in humans by giving naloxone as an unconditioned stimulus to preciptate withdrawal and pairing it with music and odors. Subsequent saline injections produced objective and subjective symptoms of narcotic withdrawal.

No matter what the cause of drug abuse or relapse, Isbell's statement that "...withdrawal is only the first and least important step in the treatment of narcotic addiction"[75] has been widely accepted.

METHADONE MAINTENANCE

The idea that methadone might be used to maintain narcotic addicts in a nonwithdrawn state while they worked out psychological and social problems in a rehabilitation program was suggested by Dole in 1965. [32] He noted the existence of a moral dilemma and quoted a U.S. Senate report as saying "...We believe the thought of permanently maintaining drug addiction with "sustaining" doses of narcotic drugs to be utterly repugnant to the moral principals inherent in our laws and the character of our people."[32] He also addressed the issue of a lack of education among physicians concerning drug addiction and noted the tendency of the medical community to avoid contact with the addict as a patient. He suggested that successful treatment of drug addiction should not focus on total abstinence from the abused substance. Rather it "...must be measured by what people do, by their adjustments to the requirements of society, and by the capacity to enjoy the small pleasures of life and meet the larger responsibilities ..."[32] He believed that "A narcotic drug should be considered to facilitate the patients reentry into society." and that "... the consistent failure of efforts to rehabilitate patients after withdrawal suggests that the addict during this phase of treatment needs pharmacological support."[32]

Dole's[33] initial trials with methadone maintenance were conducted in 1965. He stabilized 22 intravenous heroin abusers between the ages of 17 and 37 on oral methadone during the first week of phase I while on ward restriction. This involved initial doses of 10-20 mg twice a day which were increased to between 50 and 150 mg per day over the following four weeks. During the last

five weeks of phase I, they were allowed both supervised and unsupervised excursions to school, libraries, shopping and amusements. The second phase was conducted as an outpatient with daily clinic contact to receive methadone doses and leave urine specimens. Support in finding jobs, housing, and education was provided at this time until phase III was reached i.e. "...a socially normal, self supporting person."[33]

Dole found that methadone maintenance was associated with a lack of narcotic craving; blockade of heroin's agonist effects; and an ability of the clients to place themselves in situations previously associated with narcotic use. Unfortunately, however, they were not immune from emotional stresses. Both Dole[33] and Whitehead[196] have described the methadone pseudowithdrawal syndrome in which patients on adequate doses of methadone experience opiate withdrawal symptoms including malaise, nausea, yawning and sweating in the face of acute emotional stresses. Whitehead found that supportive psychotherapeutic interactions were helpful in these situations.

The success of methadone maintenance was measured by the ability of Dole's patients to become socially integrated and successful at school, work and in family relationships. At three year evaluation of the program, Dole[34] noted that out of 304 patients admitted, ninety-one percent had continued on maintenance, eight percent had been discharged for nonheroin related behavior problems and one percent had left voluntarily. Six or more months of methadone maintenance was associated with a seventy percent rate of employment or school attendance. None showed a need for psychotherapy suggesting that their antisocial behavior was a function of drug abuse not inherent psychological problems. This was confirmed by McLellan[121] and Valliant[186]. Valliant found only a ten percent rate of brief psychiatric

hospitalizations among his cohort with only four individuals carrying a diagnosis of psychosis.

In 1970, Jaffe[79] investigated the effectiveness of a totally outpatient methadone program which would eliminate the need for the initial six week hospitalization in Dole's protocol. Seventy-nine patients were followed for at least a year on an outpatient dose of 40 mg per day. At one year, fifty-two percent were still on methadone maintenance and eighty percent of this group were either employed, attending school or housewives. Twenty-one percent were no longer in treatment but maintained contact with the clinic on a weekly basis. Jaffe also compared low daily methadone doses of approximately 36 mg to higher doses of 100 mg and found a larger amount of heroin abuse in the lower group without any significant differences in arrest rate, social productivity or dropout rate. Goldstein[52] on the other hand found little difference between daily doses of 30, 50 or 100 mg even with respect to heroin abuse. With a one year outpatient survivorship of sixty-seven percent, he claimed that 50 mg was a sufficient dose and that illegal heroin use could be prevented by group and individual counseling. He stated that a one year minimum of methadone maintenance was necessary to work on employment, interpersonal relationships, etc.

Current methadone maintenance as described by Lowinson[109] consists of induction with 20-40 mg on the first day to achieve the goal of controlling abstinence. Doses are then increased by 10 mg every 3-4 days until maintenance levels are achieved. Her group uses 70-100 mg for older addicts with a longer addiction history and 30-50 mg for younger addicts. During this time, clients are given counseling for jobs, education, etc. After at least three months of daily visits and weekly urine checks, clients are considered for the privilege of take home doses.

DETOXICATION FROM METHADONE MAINTENANCE

The decision as to when a client is ready to detoxify from methadone maintenance is based on the stated reason for wanting detoxification; the amount of time in methadone maintenance (i.e. at least a year); documentation of at least six consecutive months of being employed, in school or as a homemaker; six months without drug abuse or excessive alcohol intake; and stability in emotional control and personal interactions.[86] Cushman[29] found that "...full time employment, positive motivation for detoxification, and a high degree of assimilation into the nondrug world" were correlated with successful detoxification attempts.

In comparing slow and fast reductions in methadone dosage, reports from inpatient settings have described successful detoxification in short periods of time i.e. less than one month. [86] However, Cushman[29] and Senay[159] found that in inpatient settings, a slow gradual detoxification which produces a minimum in withdrawal symptom severity was most successful. Senay suggested that methadone dosage should be reduced by three percent per week while Cushman recommended detoxification over a minimum of six months. Senay emphasized the need for education about detoxification to help allay fears that have been built up by past withdrawal experiences.

There is no consensus of opinion on the efficacy of blind vs. open techniques of detoxification. Suggestion is made that blind techniques result in less symptomatology at the end of detoxification when the patients are most sensitive to dose reduction.[86] Pharmacological support during this period can consist of diazepam for hyperirritability and chloral hydrate for insomnia.[52] However, extra methadone doses have also proved to be useful.[86]

As an estimate, only approximately fifty percent of all patients attempting detoxification are successful with at most a fifty percent abstinence rate on long term followup.[88] Reasons for failure have included anxiety about not being able to function without methadone, the severity of withdrawal symptoms or protracted abstinence. Many have turned to nonopioid drugs such as marihuana, cocaine and alcohol substituting an addiction to another.[28]

Prior to the discussion of more recent methods of detoxification, a background in the opiate receptor and endogenous peptide literature is necessary.

THE OPIATE RECEPTOR

The existence of pure opiate antagonists such as naloxone and the knowledge that the pharmacological activities of opiate compounds were stereospecific with the D(-) isomer being more potent than the virtually non active L (+) isomer suggested the presence of opiate receptors.[168] The theory of their existence was tested by Goldstein[51] in 1971. He proposed that one should be able to demonstrate stereospecific binding to an opiate receptor and was able to find subcellular stereospecific binding in the mouse brain homogenate but only at a level of 2%. Terenius[176], Simon[164, 166], Pert[130], and Snyder[167] subsequently were able to demonstrate stereospecific binding of dihydromorphine, naloxone, and etorphine to subcellular particles - specifically synaptosomes in the rat brain by using low concentrations of radioactive compounds with high specific activity, purity and affinity. This stereospecific activity which can be up to seventy to ninety percent, [166] supported the

existence of the opiate receptor. The fact that this binding was indeed to the receptor was strengthened by Snyder[167] who compared the naloxone receptor binding affinities of nonopiates and opiates of different potencies and found a good correlation between pharmacological potency and receptor affinity. Further studies revealed opiate binding to be exclusive to vertebrates and present only in nervous tissue (i.e. CNS and smooth muscle innervation). The guinea pig ileum and mouse vas deferens have become the classic models used to study this system.[166]

Once the opiate receptor was identified it became possible to map its location within nervous tissue. Some early studies by Kuhar[98] in the rat brain showed regional variation with a high degree of binding in the corpus striatum and virtually none in the cerebellum. Kuhar[98] and Snyder[167] then mapped receptors in the rhesus monkey and human brain using the radioactive agonist dihydromorphine. The human and monkey brains showed similar distributions of receptors with up to a 30 fold regional variation. Most binding was present in the amygdala, thalamus, head of caudate, hypothalmus, periaqueductal midbrain, putamen and frontal poles of the cerebrum. As in the rats, little uptake was noted in the cerebellum. Later experiments by Simon[166] using etorphine in the human brain confirmed Kuhar's findings. (For details see 98,166,167). To determine if opiate receptors were associated with any known transmitters, nonadrenergic, cholinergic, and serotoninergic pathways were destroyed. The subsequent lack of change in opiate receptor binding led to the conclusion that the opiate receptor was "...not a unique component of the axons or nerve endings of anyone of these neuronal tracts".[98]

Another dimension was added to the in vitro experiments described above when autoradiography enabled researchers to map receptor distribution after in

vivo administration of markers. Pert[131] used ^{3}H-diprenorphine a high affinity antagonist and demonstrated low cerebellar binding with high binding in the caudate-putamen, locus coeruleus, zona compacta and substansia gelitinosa of the spinal cord of the rat. Extensive autoradiographic studies were later done by Atweh[5,6,7] who mapped opiate receptors in the rat brain, spinal cord, medulla and brain stem with etorphine and diprenorphine.

In other studies, Simon[166] found saturable kinetics and proved a finite number of receptor sites existed. Höllt[68] showed that receptor occupancy by naltrexone was associated with withdrawal behavior in morphine tolerant/dependent mice. In addition, he found that there was an in vivo correlation between binding and pharmacological effects by observing that etorphine induced analgesia could be reversed by naltrexone. The largest decrease in etorphine receptor occupancy corresponded to the etorphine dose range (3-300µg/kg) at which the analgesic effect was absent. In other studies, the association between opiate receptor rich regions and analgesia was demonstrated by injecting morphine into the brains of monkeys.[98,167] It was of interest that both the anatomical location and agonist pharmacological effects were seen in the limbic system - a region believed to control euphoria and attenuate reactions to pain.[166] Finally, Bird and Kuhar[99,11] applied morphine ionotophoretically to the locus coeruleus - a region known to possess a high density of opiate receptors. They found a decrease in the spontaneous firing rate in the locus coeruleus which could be both reversed and prevented by naloxone. In summary, the in vitro and in vivo results had been correlated and the necessary criteria for demonstrating the existence of opiate receptor binding i.e. -saturability, stereospecificity, regional distribution and association of apparent binding with pharmacological effect had been met.

ENDOGENOUS OPIATE PEPTIDES

The convincing identification of an opiate receptor led to speculation about the existence of an endogenous opiate substance. Akil and Mayer's[3] findings that electrical stimulation of the central grey of rates produced analgesia which could be partially reversed by naloxone was suggestive of an endogenous opiate compound. In 1975, Hughes[73] demonstrated the existence of an endogenous substance from pig brain which acted as an agonist in the mouse vas deferens and guinea pig ileum and produced naloxone and naltrexone reversible inhibition of electrically induced contractions. Terenius[177] and Pasternak[129] identified a compound in the calf and rat brain which acted like an endogenous ligand by inhibiting the opiate receptor binding of naloxone and dihydromorphine. In addition, it had an anatomical distribution similar to the opiate receptor, showed inhibition of binding with sodium and enhancement with magnesium as expected for an agonist;[130,165,166,167,168] and was located in synaptosomal fractions. Hughes[72] further characterized the pig brain extract which he named enkephalin as being composed of two parts peptides differing in the carboxyl amino acid. Named met-enkephalin and leu-enkephalin, these peptides showed naloxone inhibited agonist activity the guinea pig ileum and mouse vas deferens. The calf brain extract was studied by Simantov[162,162] who found it to be met-enkephelin and leu-enkephalin - the same peptides identified by Hughes in the pig brain.

Another opiate compound was identified in bovine pituitary extracts by Teschmacher and Goldstein[179] and in crude ACTH extract by Cox[24]. This compound exhibited the agonist properties of naloxone reversible inhibition of electrical stimulation of the guinea pig ileum and mouse vas deferens; inhibited

binding of etorphine at synaptic membranes; and showed sodium inhibition effects. Furthermore, it resembled β-lipotropin (β-LPH) - a pituitary compound identified in 1964 by Li[104,105] in ACTH extract from sheep pituitary gland. Cox[25] further characterized this peptide showing that β-LPH (amino acids 1-91) had no opioid activity while the 61-91 fragment which contained the 61-65 sequence of enkephalin did possess opioid activity in the guinea pig ileum as well as stereospecific inhibition of etorphine binding in brain homogenates. Bradbury[13] confirmed this finding. Other investigators identified α-endorphin (amino acids 61-76) and γ- endorphin (amino acids 61-77) as active fragments. The 61-91 fragment referred to as β-endorphin is the most active. [166] The discovery of an inactive large peptide chain containing smaller active fragments led Cox[25] to propose that β-LPH might be a prohormone similar to proinsulin.

Attempts at mapping the distribution of these endogenous compounds by Watson,[192,193] Bloom, [12] Snyder,[168,169] and Elde[36] showed a predominantly different distribution for β-endorphin and the enkephalins. Attempts at selective mapping of met-enkephalin using antisera to met-enkephalin which did not cross-react with leu-enkephalin or endorphin failed to demonstrate any differences in the CNS distribution of the two enkephalins. Enkephalin was also demonstrated in peripheral regions by Schultzberg[157] who found enkephalin immunoreactivity the sympathetic ganglia of the guinea pig and rat. The different neuronal pathways and origins of the endorphin and enkephalins were suggested by the fact that unlike the endorphins, the enkephalin distribution appeared to be parallel to that found for the opiate receptor. Furthermore, antisera to ACTH stained β-endorphin/β-LPH cells but not enkephalin cells suggesting that endorphin was derived from an ACTH precursor while

enkephalins were not despite some common amino acid sequences.[12] At this point, however, the relationship between met enkephalin and β-endorphin is far from certain especially since there is some overlap in their distribution.[192]

The next studies turned to the role of these compounds as endogenous opiate agonists. Hughes'[72] initial studies had demonstrated the effects of the enkephalins on peripheral organs finding met-enkephalin to be 20 times as potent as morphine while leu-enkephalin was 10 times as potent in the mouse vas deferens. In the guinea pig ileum, model met-enkephalin was as potent as morphine and leu-enkephalin possessed one-fifth the potency of morphine. Cox[25] demonstrated β-endorphin agonist activity in the guinea pig ileum finding it to be equipotent to met-enkephalin. Lord[108] found that β-endorphin was equipotent in the guinea pig ileum and mouse vas deferens and inhibited leu-enkephalin and naloxone equally well in the guinea pig brain. Further comparison of the endorphins and enkephalins showed α-endorphin, met-enkephalin and leu-enkephalin to be more potent than β-endorphin in the mouse vas deferens while α-endorphin and leu-enkephalin were less active than met-enkephalin and β-endorphin. The later two peptides were equipotent in the guinea pig ileum.

Turning to central effects, Simantov[162] found that both met- and leu-enkephalin decreased dihydromorphine binding in the rat brain equally well while met-enkephalin was twice as potent as leu-enkephalin in decreasing naloxone binding. In addition, the effect of sodium in reducing agonist binding was two times greater for leu-enkephalin than met-enkephalin implying that met-enkephalin may have more antagonist properties. Chang,[20] Büscher,[17] Bradley[14] and Graf[54] studied the properties of enkephalins in both brain homogenates and after direct injection into brain tissue in vivo. Chang[20]

showed that met-enkephalin had one-half the affinity of morphine while leu-enkephalin had one-seventh the affinity in opiate receptor binding studies. Direct injection of the enkephalins and morphine into the periaquaductal grey of rats showed the leu-enkephalin had virtually no analgesic effect and met-enkephalin was much less potent than morphine requiring high doses to produce short lived naloxone reversible analgesic effects. Bradley[14] injected met-enkephalin into single neurons in the rat brain stem and found that met-enkephalin had naloxone reversible depression of seventy percent of neurons which were also depressed by etorphine and morphine. Büscher[17] and Graf[54] performed intracerebroventricular injections and confirmed the fact that both enkephalins have faster acting and shorter lived analgesic actions than morphine. Morphine analgesia was greater than met-enkephalin which was greater than leu-enkephalin.

The evanescent action and weak potency of the enkephalins was thought to be due to their rapid enzymatic degradation in the brain.[20,133] Pert[133] synthesized the compound [D Ala^2]-met-enkephalinamide which proved to be less susceptible to degradation and produced longer lived analgesia when injected into the rat brain. Craves[26] criticized the use of such analogues claiming that their antinociceptive potency is due to some undefined property. He found differences from the natural peptides in lipid partitioning, potency in both the guinea pig ileum and mouse vas deferens models and interactions with brain opiate receptor sites. Furthermore, he questioned the theory of rapid enzymatic degradation calculating the half life of met-enkephalin in vivo to be 3.9 minutes. This period is longer than would be expected for transient analgesia effects.

Studies on βendorphin were conducted by Tseng,[182,183] Loh,[107] Jacquet,[77] Bloom,[12] and Graf[54]. Jacquet and Loh injected β-endorphin into the periaqueductal grey of rats and found that β-endorphin had greater naloxone blocked/reversible analgesic activity than morphine. Tseng and Graf performed both intravenous and intracerebroventricular injections showing the production of naloxone reversible analgesia with β-endorphin analgesia greater than morphine which was greater than met-enkephalin. The β-endorphin analgesia was different than enkephalin in that it had a longer latent period and duration. Bloom noted naloxone reversible electroencephalogram (EEG) changes in rats treated with intracerebroventricular β-endorphin. These EEG changes were more pronounced for β-endorphin then met-enkephalin. Morphine-like tolerance and dependence were produced by β-endorphin as demonstrated by naloxone precipitated withdrawal symptoms, cross tolerance to morphine and attenuation of analgesic and EEG responses.[12,107,183] The development of tolerance/dependence and naloxone induced withdrawal symptoms has also been observed with enkephalin.[169]

Nonanalgesic responses to the endogenous peptides were studied by Bloom,[12] Tseng,[183] Jacquet,[77] and Wei[195]. β-endorphin appeared to elicit more pronounced behavioral responses than the enkephalins or α-endorphin during intracerebral injections. Naloxone revisible catatonia, sedation, and rigidity were seen with β-endorphin while morphine was more often associated with hyperactivity. Finally, the enkephalins produced an increase in locomotor activity not observed with β-endorphin.

The apparent naloxone reversible analgesia produced by the endogenous peptides led investigators to postulate that naloxone should alter pain perception in humans by competing for receptor sites with these supposed

endogenous ligands. The studies which had supplied some indirect evidence for a role of endogenous peptides in pain perception were Pomeranz[136] who demonstrated naloxone reversible analgesia in mice during acupuncture; Mayer[120] who showed that naloxone antagonized the elevated pain threshold in humans subjected to acupuncture; and Hosobuchi[69] who found naloxone reversible attenuation of pain in humans during electrical stimulation of the brain. However, Grevert[56] was not able to find any naloxone induced difference in the pain ratings of individuals subjected to ischemia and cold water immersion. Buschbaum[16] postulated that there might be individual variation in endogenous peptide levels. He divided people into pain sensitive and insensitive groups and demonstrated that naloxone administration to the pain insenstive group increased the perception of pain produced by electric shocks. Levine[103] went one step further and showed that naloxone could increase existing pain from dental extraction. He concluded that noxious stimuli might precipitate the release of endogenous peptides which were then antagonized by naloxone.

MULTIPLE OPIATE RECEPTORS

The differences in enkephalin, endorphin and morphine binding in the mouse vas deferens and guinea pig ileum preparations; the varied behavioral responses elicited by these compounds; and the existence of pure antagonist, pure angonist and mixed antagonist compounds suggested the existence of multiple heterogenous opiate receptors with compounds acting at several different sites. Martin[118] did extensive studies on the chronic spinal dog and suggested the presence of three receptors which produced different

physiological responses. These included μ for the agonist morphine; κ for the mixed antagonist/agonist ketocyclazocine which neither suppressed the morphine abstinence syndrome nor precipitated significant withdrawal symptoms; and σ for SKF 10047. Lord[108] analyzed guinea pig brain homogenates and the mouse vas deferens and guinea pig ileum models finding that the guinea pig ileum contained μ and κ receptors with a predominance of μ receptors while the mouse vas deferens had δ and μ receptors with a predominance of δ receptors. The presence of the fourth receptor, δ , was also suggested by Kosterlitz[95] who demonstrated that enkephalin and β-endorphin can interact with the μ receptor in the guinea pig ileum but will show predominantly δ receptor interactions in the mouse vas deferens. Schulz[156] was able to separate the μ and δ receptor activities in the mouse vas deferens by using sufantanyl, a selective μ receptor agonist, and DAla^{2}Dleu^{5}enkephalin a δ receptor agonist. He demonstrated selective tolerance for each receptor without evidence of cross tolerance. The δ receptor in the mouse vas deferens resembled the leu-enkephalin receptor in guinea pig brain[96] and the presumed almost pure δ population in neuroblastoma cells[21]. The possibility of a fifth receptor has been noted in the rat vas deferens.[62] This receptor exhibits excellent β-endorphin agonist activity, slight enkephalin activity and negligible morphine activity. In another classification scheme, Terenius[178] suggested that opiate receptors could be broken down into morphine, antagonist and opiate peptide sites with the antagonist properties of the compounds determining their affinity for these sites. Indeed, Synder[168,169] demonstrated that the greater the antagonist properties of a compound the greater its affinity for met-enkephalin sites as opposed to naloxone/dihydromorphine labeled sites. Finally, Herling[61] demonstrated interspecies variation in opiate

receptor heterogeneity. Despite all the evidence suggesting the existence of multiple receptors one must keep in mind the excellent point made by Adler[1] who suggested that we will not be able to prove the existence of these receptors until selective antagonists are discovered.

The classification scheme can be summarized as follows:

1.	μ	CNS, guinea pig ileum, mouse vas deferens
2.	κ	CNS, guinea pig ileum
3.	σ	CNS
4.	δ	mouse vas deferens, neuroblastoma, CNS-enkephalin
5.	#5	rat vas deferens

(modified from Terenius[178])

THEORIES ABOUT OPIATE TOLERANCE AND DEPENDENCE

There are several theories concerning the possible biological mechanism and consequences of opiate tolerance and dependence. The first theory postulates that there is a change in the number or the affinity of opiate receptors. The results of these experiments have provided conflicting results. Pert[132] found an increase in opiate receptor binding with chronic morphine pellet implantation. However, the same amount of binding was seen two hours post-implantation as at 108 hours. This was a time period during which tolerance had increased by a factor of five. Furthermore, the maximal increase in binding occurred within five minutes which was much sooner than tolerance and dependence had peaked. Pert also made the observation that antagonists

were up to 1000 times more potent in increasing receptor binding than agonists. In fact, the greater the antagonist properties of a compound the greater its effect. These findings have been confirmed by Herz,[62] Lahti,[100] Schultz,[155], and Tang[174] who observed an increase in receptor number not affinity following antagonist treatment. Since changes in the sodium concentration of the assay abolished the receptor enhancement by agonists, Pert concluded that there were no receptor changes in opiate tolerance/dependence. He interpreted his results as demonstrating the displacement of endogenous opiates by exogenous opiates which would make the receptors available for in vitro labeling. Simon,[166] Höllt,[67] and Dum[35] also failed to demonstrate a change in opiate receptor binding or affinity in tolerant vs. naive animals using brain homogenates with in vivo and in vitro techniques. The only studies which did find opiate receptor changes were those conducted by Davis[31] who used brain slices as opposed to brain homogenates. She documented a decline in opiate binding secondary to decreased affinity which persisted for up to four days after withdrawal in rats chronically treated with morphine and etorphine.

The second theory suggests that chronic exposure to exogenous opiates would result in a decline in the level of endogenously produced peptides possibly by feedback inhibition[53] and/or an increase in endogenous peptide inactivation[110]. Using a sensitive specific radioimmunoassay, Childers[23] failed to find an effect of chronic morphine treatment in rats on met-enkephalin or leu-enkephalin levels. Bergström,[9] on the other hand, found no effect on enkephalin levels in rats after a single acute dose of morphine. However, chronic treatment while failing to show a change within two hours of the last dose, did show decreased enkephalin levels at 24 hours. This was followed by a return toward baseline with insignificantly decreased enkephalin levels as

compared to the control and two hour group at 48 hours. The maximum decline in brain enkephalin levels corresponded to the peak in withdrawal symptomatology suggesting that the abstinence syndrome may represent an imbalance in the enkephalin system. Although Childers did precipitate withdrawal in his studies using naloxone, he measured enkephalin levels within 60 minutes which possibly was too short a period of time according to Bergström's study. To date, no one has developed a method to measure enkephalin turnover which certainly could be affected. The possibility that enkephalin is more rapidly degraded in chronic morphine addiction is suggested by Malfroy.[110] He demonstrated a selective increase in the activity of a high affinity enkephalin degrading peptidase in the particulate fraction of mouse striatum following chronic morphine treatment. The distribution of this peptidase showed regional heterogeniety paralleling the previously determined enkephalin peptide distribution.

Other researchers have suggested that endorphin levels may be affected by chronic opiate exposure. The association between ACTH and β-endorphin was noted during mapping studies as previously described. Guillemin[59] later demonstrated the concomitant secretion of ACTH and β-endorphin from the pituitary gland of rats. Plasma and pituitary concentrations of these compounds paralleled each other making the theory of β-lipotropin as a common precurser to ACTH and β-endorphin plausible. Subsequently Volovka[187] found that naloxone increased plasma ACTH and cortisol levels in men who did not have a history of opiate addiction and suggested that the endogenous opiates which were presumably displaced by naloxone might regulate ACTH and by association endorphin/β-lipotropin secretion through feedback inhibition. Ho[64,65] went on to demonstrate that rats addicted to morphine for three or

more months had less β-endorphin immunoreactivity in their brain tissue than controls. He also demonstrated that both serum ACTH and serum β-lipotropin/β-endorphin levels in heroin addicts were lower than controls. Finally, Gold[48] showed that methadone infusion can lower plasma cortisol levels in humans. Further studies with methadone addicts who had undergone clonidine detoxification showed that naltrexone failed to elicit the marked rise in plasma cortisol levels as observed in Volovka's normal human subjects. In fact, the small increase observed was statistically insignificant when compared with baseline values. Gold proposed that these results reflected decreased ACTH/β-lipotropin/β-endorphin reserve levels in methadone addicts as compared to controls and that the withdrawal syndrome may represent an inadequate endogenous endorphin supply which has been suppressed by exogenous opiates. This low reserve would become apparent when the exogenous opiate supply was abruptly removed.

The third theory concerns the role of central nonadrenergic neurons in withdrawal and is the basis of the clinical trials with clonidine. An associationbetween increased sympathetic activity and opiate withdrawal was noted at least as far back as 1938. Kolb believed that

> ... the functions of the sympathetic nervous system are depressed by morphine. In chronic users there is a reaction against this depression that tends to restore the functions to normal... When morphine is withdrawn the reactive mechanism designed to counteract poisonous doses of it continues to work... This causes powerful stimulation of certain functions under the control of the sympathetic - hence, the sweating, goose-flesh... increased blood sugar from the outpouring of adrenalin, raised blood pressure, etc.[91]

As will become evident in the discussion to follow, recent research has shown that Kolb was closer than others before him in proposing a satisfactory mechanism of drug addiction and withdrawal.

As reviewed by Langer,[101] the noradrenergic transmission system is believed to be controlled by α and β receptors located both pre- and postsynaptically. Nerve stimulation causes noradrenaline release which at low concentrations would activate presynaptic β receptors and further increase noradrenaline release via cyclic AMP. However, when the concentration of noradrenaline in the synaptic cleft reaches a certain threshold, negative feedback inhibition would become important and noradrenaline would activate presynaptic α receptors and inhibiting noradrenaline release. This action is believed to be mediated through reduced availability of calcium for stimulus -secretion coupling.[171] Based on studies outside the CNS with various receptor antagonists and agonists, Langer demonstrated that pre- and postsynaptic α receptors were different. As such he proposed the classification of α1 receptors as postsynaptic receptors which controlled responses at the effector organ and α2 as presynaptic receptors which mediated noradrenaline release during nerve stimulation.[101]

The development of clonidine, a presumed α2 receptor agonist, has aided in much of the research on α receptors. Clonidine's actions on α receptors were noted in experiments showing that it depressed the electrically stimulated release of norepinephrine from rat cerebral cortex slices and mouse atria and decreased norepinephrine turnover in the brain.[171,37,18] The question of whether clonidine is a pre- or postsynaptic α agent has been hotly debated. Haeusler[60] has argued for a postsynaptic

location while Starke[171] found that clonidine can act at both pre- and postsynaptic sites but will act preferentially at the presynaptic site. In general, clonidine is considered to be an $\alpha 2$ receptor (i.e. presynaptic). Part of the problem in the characterization of clonidine lies in the controversy about the location of $\alpha 2$ receptors in the brain. Young[203] recently attempted light microscopic autoradiographic localization of $\alpha 2$ receptors in the rat brain but failed to resolve the issue. He concluded that the $\alpha 2$ receptors might be located both pre- and postsynaptically in the CNS.

In studies aimed at mapping monamines in the CNS, Dahlström[30] demonstrated the presence of a tightly packed group of nerve cells in the locus coerulus (LC) which were characterized by being almost entirely composed of norepinephrine. The LC is a nucleus in the anterior pons which has projections to the ipsilateral cerebral cortex, hippocampus[92,94] and cerebellum[19] and receives projections from the medulla.[19] Studies by Korf, Aghajanian and Roth demonstrated that electrical stimulation of the LC increased levels of MHPG sulfate, a norepinephrine metabolite, in the cortex and hippocampus of rats. Conversely the destruction of the LC caused an 80% reduction in norepinephrine levels and a 70% reduction in MHPG sulfate in the ipsilateral cortex and hippocampus.[92] They proposed that since stimulation of the LC caused a reduction in cortical norepinephrine (NE), impulses originating in the LC and flowing through adrenergic pathways must cause an increased turnover in NE stores. Further evidence of increased turnover lay in the demonstration that stimulation induced increases in NE turnover could be abolished by transection of the dorsal pathways from the LC to the cortex and hippocampus. Thus the NE content of the cortex appeared to be related to LC activity.[93]

Among the multiple presynaptic receptors in noradrenergic nerve endings is the opiate receptor. This receptor can inhibit transmission at adrenergic nerve endings when acted upon by opiate receptor agonists.[101,171] A possible relationship between the LC and opiate compounds was proposed with the discovery that it contained a high density of opiate receptors[131] as well as β-lipotropin / β-endorphin[12] and met-enkephalin reactivity[99,193]. Furthermore, studies by Korf,[94] Young,[202] Kuhar,[99] and Bird[11] demonstrated that both morphine and met-enkephalin could produce selective naloxone reversible LC depression.

The locus coeruleus also possesses α receptors. Cedarbaum[18] found that the α antagonist piperoxane increased the rate of spontaneous LC firing in rat brains while clonidine, norepinephrine and epinephrine reduced the level. Furthermore, piperoxane was able to prevent and/or reverse the clonidine inhibition. Norepinephrine and epinephrine inhibition was postulated to be through actions at presynaptic α receptors which act as autoreceptors as per Langer. The LC α receptors were further characterized by Cedarbam[19] as being of the α2 type since the postsynaptic α agonist phenylephrine had only weak inhibitory effects on LC firing. Furthermore, clonidine proved to be α the most potent of the α agonists in the LC. Young's[203] autoradiographic studies were consistent with Cedarbaum's results. He found a predominance of α2 receptors in the LC with only very low densities of α1 receptors.

Aghajanian[2] was able to convincingly demonstrate that the α and opiate receptors in the LC were separate despite having similar qualitative actions. Using single cell recording and microionotophoretic techniques he found that acute morphine injections produced naloxone inhibited LC

depression and that clonidine was able to depress LC activity even in the presence of naloxone blockade. Similarly, blockage of α receptors with piperoxane inhibited clonidine's LC depressant actions but did not alter morphine effects. He went on to demonstrate the development of tolerance to morphine, finding that LC firing was decreased 24 hours post-morphine pellet implantation in the rat brain but had returned to baseline within 4-5 days. Finally, naloxone induced withdrawal in morphine dependent rats was accompanied by clonidine reversible increased LC firing which was consistent with the hypothesis of a hyperadrenergic state during withdrawal which might be effectively treated with the nonopiate compound clonidine. Further evidence for this later idea came from Crawley, Laverty and Roth who demonstrated that clonidine reduced the increase in NE turnover in the brains of morphinized rats undergoing naloxone induced withdrawal.[102] This NE turnover appeared to be associated with LC activity since MHPG levels in brain regions innervated by the LC were increased during naloxone precipitated withdrawal. It was of interest that clonidine also reversed these changes.[27]

Studies by Redmond and Huang have concentrated on the role of the locus coeruleus in nonhuman primates. Their findings would presumably be applicable to man. Initial work on the stumptail macaque confirmed the findings already described for other animal systems. Namely, destruction of the LC lowered MHPG and norepinephrine levels in the cortex and hippocampus with seventy-one to eighty-one percent depletion following a single lesion and eighty to ninety percent with bilateral lesions. Therefore, most of the norepinephrine in the macaque cerebral cortex appeared to come from the LC.[70] In addition, naloxone treated morphine tolerant primates

showed increases in brain and plasma MHPG levels as would be expected during the hyperadrenergic withdrawal state.[143]

In subsequent studies, this group investigated the effects of LC stimulation[140], destruction[141], and piperoxane[43,144] administration noting that LC stimulation and piperoxane produced similar behaviors which resembled primate reactions to human threats and opiate withdrawal while destructive lesions attenuated these behaviors. The behaviors included yawning, chewing, scratching, startling, struggling, wringing of hands, pulling of hair or skin, tongue movements, chair grasping, self mouthing, pupillary dilatation, piloerection, increased blood pressure, increased heart rate, and alerting.[145] Intravenous clonidine was found to either depress or block the behavioral effects of LC stimulation and piperoxane[43,71] while naloxone was able to reverse the depressant affects of morphine and met-enkephalin on these induced behaviors.[142] Thus, the LC appeared to be involved in "anxiety-fear" behavior[140] and possibly the hyperadrenergic state of opiate withdrawal.[145]

Using the information discussed above and some more recent developments, several authors have hypothesized about the events which may occur during morphine dependence, withdrawal and post-detoxification states. Llorens[106] found that chronic morphine treatment in rats caused hypersensititivity to norepinephrine with a fifty percent increase in cyclic AMP stimulation and a nineteen percent increase in the number of β adrenergic receptors. This was not accompanied by a change in their affinity. He postulated that morphine causes a "disuse hypersensitivity" such that the depressant effect of morphine on noradrenergic transmission is compensated for an increase in the number of postsynaptic β receptors. In

abstinence, inhibition of noradrenergic neurons is abruptly stopped flooding an excess number of receptors with a nondepressed quantity of transmitters. This adds to LC hyperactivity and possibly as Gold suggests[47] a lack of endogenous opiate peptides to create the state of increased sympathetic activity seen during withdrawal. Nathanson[125] confirmed Llorens' findings by demonstrating postsynaptic supersensitivity in primates. He went one step further suggesting that the noradrenergic hyperactivity in withdrawal might cause a reciprocal subsensitivity of noradrenergic receptors post withdrawal. He found that both morphine withdrawal and piperoxane antagonist actions produced a fall in adenylate cyclase activity below that seen in either controls or the chronic morphine state. He suggested that this is consistent with down regulation or β receptor subsensitivity and might explain the protracted abstinence syndrome described by Martin.

The studies oulined above as well as those of Fielding[38] who demonstrated clonidine suppression of the morphine abstinence syndrome in rats led to investigations into the use of clonidine for the human opiate withdrawal syndrome.

CLINICAL APPLICATIONS OF CLONIDINE

Clonidine was synthesized in 1962 and initially used to treat patients with moderate to severe hypertension.[134] Preliminary studies on animals had shown that intravenous injections produced a transient increase in blood pressure which was believed to be secondary to peripheral α adrenergic stimulation. This was followed by hypotension and bradycardia with decreased cardiac output and occasionally decreased peripheral resistance. Increased vagal

activity was also noted and felt to contribute to the bradycardia. The lack of a tachycardic response suggested the presence of α agonist activities without β agonist actions.[90] These cardiovascular effects appeared to be mediated by depressed sympathetic activity since depletion of sympathetic amine stores either abolished or diminished clonidine's hypotensive actions.[40] Furthermore, these effects appeared to be centrally based at the level of the medulla, possibly in the nucleus solitarius,[203] since intracisternal injections were more effective than intravenous ones and transection below the level of the medulla abolished clonidine's actions.[89,153,154] Finally, clonidine was noted to have renal actions suppressing renin secretion either by decreasing centrally mediated renal sympathetic tone[146] or acting on α adrenergic receptors in the kidney parenchyma itself.[194] Lowered renin levels appeared to cause lower aldosterone levels thereby preventing water retention and adding to its antihypertensive action.[194]

In man,[134] the onset of clonidine's antihypertensive effect is seen at 30 minutes reaching a maximum at 2-4 hours and lasting up to 24-26 hours. Side effects at usual dosages of 0.2 - 2.4 mg/day include transient sodium retention, drowsiness, lethargy, dry oral mucosa and potentiation of insulin induced hypoglycemia. Clonidine was also noted to have a withdrawal syndrome when abruptly stopped[134,147,173] with symptoms of insomia, anxiety, nervousness, headache, abdominal pain, nausea and vomiting occurring within 18-24 hours and elevated blood pressure in 24-48 hours. This is associated with increased levels of plasma norepinephrine and urinary catecholamines at 24-72 hours and is thought to be secondary to hyperactivity of the sympathetic nervous system. It is seen mostly in individuals whose daily doses exceed 1 mg and can be prevented by a 2-4 day taper.

CLONIDINE TRIALS IN HUMAN OPIATE WITHDRAWAL

Initial studies on the use of clonidine were conducted by Gold, Redmond, and Kleber[44,45,46] in 1978 on five individuals who had taken methadone for at least six months in the 15-50 mg dose range. After an initial 36 hour period of methadone abstinence, they were treated as inpatients on a locked ward in a placebo controlled study utilizing initial clonidine doses of 5µg/kg. Withdrawal symptom ratings were conducted every 30 minutes and vital signs were closely followed. A reversal of baseline withdrawal symptoms was observed within 90 minutes with both systolic and diastolic blood pressure drops from 124/85 to 106/69 manifested by 120 minutes. All participants expressed subjective relief and related that clonidine had stopped the sensation of "kicking" which had been present on admission. This inpatient study was followed by a week long outpatient trial of 5µg/kg twice a day. Patients were observed daily failing to show any apparent change in abstinence ratings. Most complaints consisted of sluggishness and insomnia. The withdrawal symptoms did not recur when clonidine was stopped nor were there any manifestations of the clonidine withdrawal syndrone.

A more sophisticated inpatient study was later conducted by this same group[184] on nine opiate addicts (7methadone, 2 dilaudid). This was a double blind study where patients were told that they would be given methadone, clonidine or placebo at 9AM, 1PM, 5PM, and 9PM. Clonidine was started at doses of 1.5-5 µg/kg when mild abstinence appeared and increased appropriately for symptomatology stopping when systolic blood pressure fell below 85. All patients were started on clonidine within 36 hours of methadone withdrawal and

reached an average peak dose of 13.4μg/kg/day. Tapering of clonidine over a 2-5 day period was conducted when withdrawal symptoms had been absent for 24-48 hours. The clonidine therapy lasted for eight days and naltrexone was safely begun in all participants on the third post-clonidine day without a recurrence of abstinence symptoms. Everyone stated that the abstinence symptoms were less severe with clonidine than in other detoxification attempts. Symptoms which were most prominent included aching of bones and muscles and insomnia. There were no syncopal episodes or evidence of severe bradycardia or hypotension. Thus clonidine appeared to safely suppress the onset of withdrawal symptoms. Furthermore, followup of this group at three months did not reveal the presence of any physiological symptoms.

The clonidine withdrawal technique was refined by Gold[50] in a 14 day inpatient study which included ten participants with methadone maintenance in the 10-50 mg range. Successful detoxification could be achieved with initial doses of 6 μg/kg two times per day for the first day after 36 hours of abstinence. This was followed by a nine day course of 17 μg/kg/day divided in three doses and a taper over days 11, 12, and 13 by fifty percent per day. Naloxone challenges on day 14 were negative for all patients indicating successful detoxification. Clonidine doses did have to be titirated individually in this study as dizziness became an occasional problem requiring single doses to be held. One further study by Gold[49] proved that this method could be applied to individuals on low (14 mg), medium (50 mg) and high (75 mg) doses of methadone. All were able to achieve successful detoxification although the 50 mg and 75 mg groups experienced more symptoms.

Washton and Resnick[188,190] have conducted successful outpatient studies. Initial studies included 70 patients who had methadone habits in the 5-

40 mg range or a heroin habit in the $10-$150 range. Twenty patients were treated with clonidine and a methadone taper of 5-10 mg per week. The others were treated with just clonidine following abrupt termination of methadone or heroin. Doses of clonidine were started at 0.1 mg every four to six hours for the first day with increases of 0.1-0.2 mg to a 1.2 mg maximum each day for ten days. Doses were individualized based on blood pressure and symptomatology. They found that abrupt cessation of opiates proved to be more successful than methadone taper in conjunction with clonidine detoxification and stressed the importance of individual dose determination to minimize symptoms of lightheadedness and lethargy. In addition, they found that a clonidine taper was necessary to prevent headaches and return of withdrawal symptoms.

In another study,[189] this group compared outpatient clonidine detoxification to a slow methadone taper of 1 mg per day. Neither method appeared to be more successful. The only difference noted was that clonidine treated patients experienced withdrawal symptoms during the first days of withdrawal while the methadone taper participants did not have symptoms until the end of the study when the methadone doses were very small.

The latest study by Charney and Kleber[22] was conducted on 21 patients with a methadone maintenance range of 10-20 mg and demonstrated an eighty percent success rate. The protocol involved 10-11 days of individually adjusted clonidine doses with a mean peak of 6.8 µg/kg and a range of 10-22.2 µg/kg on day five when symptom ratings were maximal. Doses were given three times per day and tapered over the last 3-4 days of treatment without evidence of a reemergence of withdrawal symptoms. Statistically significant but clinically insignificant changes were recorded in standing blood pressure while the

predominant withdrawal symptoms included anxiety, restlessness, insomnia and muscle aching.

LOFEXIDINE

The major drawbacks of clonidine therapy are its antihypertensive and sedative actions. Recently another α agonist, lofexidine, was tried because it demonstrated less hypotensive and sedative effects, and was shown to suppress withdrawal in morphine dependent rats.[160] Washton and Resnick[191] conducted an outpatient trial on 15 methadone addicts whose maintenance doses were 10-25 mg. Loxefidine was begun while on methadone and doses were individually determined according to symptomatology. Methadone was stopped on the second day and lofexidine was continued for a total of eleven days including a taper. On day eleven, a naloxone challenge test was given to all participants who had remained abstinent and naltrexone therapy was started if the challenge was negative. These subjects showed no evidence of oversedation, lightheadedness, blood pressure drops or uncontrolled abstinence symptoms. As with clonidine, insomnia, lethargy, and muscle and bone pain still persisted. Washton and Resnick suggested that the less prominent hypotensive and sedative effects might make lofexidine preferable to clonidine in opiate withdrawal. The usefulness of this agent awaits further clinical trials. In addition, its availability is a problem. Unlike clonidine, it is not currently an FDA approved drug. The company has not attempted to seek this approval because of its relatively poor antihypertensive effects.

OPIATE ANTAGONISTS

Based on Wikler's conditioning theories, research was directed toward the use of opiate antagonists in extinguishing possible conditioned withdrawal responses from exteroceptive and interoceptive stimuli as well as helping to minimize drug seeking behavior during the protracted abstinence syndrome described by Martin. Original studies with nalorphine, a mixed antagonist/agonist, noted its ability to precipitate abstinence in morphine dependent individuals. It appeared to have strong analgesic actions and low dependence producing properties. However, its short duration of action and numerous side effects including dysphoria, hallucination, unsteadiness, and feelings of drunkiness made it undesirable[82,114]

In the mid 1960's, Martin et al.[112,113] began investigating the use of another mixed agonist/antagonist-cyclazocine. This drug also precipitated abstinence symptoms. However, it had a longer duration of action than nalorphine lasting up to 12 hours with a peak at 2-3 hours, and was 10-20 times more potent than nalorphine. Tolerance developed to its agonist actions but not to its antagonist properties. Furthermore, it prevented or diminished both the euphoric and dependence producing properties of morphine. Side effects were similar to those of nalorphine with sedation, ataxia, hallucinations, etc. Since tolerance developed to these symptoms, cyclazocine was preferred over nalorphine by patients. Finally, a definite but mild abstinence syndrome was observed when cyclazocine was abruptly stopped but did not lead to drug seeking behavior.

Jaffe[78] conducted the initial clinical trials with cyclazocine finding that it would be taken voluntarily by a group of well motivated addicts. Subjects

were slowly inducted onto the drug 48-72 hours after methadone withdrawal having proven successful detoxification with a negative nalorphine test. Jaffe found that his patients liked the drug claiming that they had more energy and a decreased desire for narcotics. When patients tested the drug with heroin some were very relieved to discover that it did indeed minimize or completely block heroin's euphorigenic effects. Jaffe even suggested the use of cyclazocine for extended periods of time since maintenance therapy had actually been requested by some patients.

Kleber[84,85] conducted a long term outpatient trial with cyclazocine. He found that the side effects experienced during induction were a problem but that naloxone could control these symptoms. The combination resulted in an eighty percent induction rate. This trial was conducted in a low intervention treatment setting in which subjects attended clinic daily for their cyclazocine doses and had scheduled group therapy sessions two nights a week.

The search for antagonists with less agonist properties and fewer objectionable side effects led to the development of naloxone. Foldes[39] specifically investigated the respiratory and circulatory effects of naloxone as compared to nalorphine and oxymorphine. He found that naloxone itself had no respiratory depressant effects and was more effective than nalorphine in antagonizing respiratory depression caused by oxymorphine. However, naloxone did cause pulse rate and systolic blood pressure depression similar to nalorphine and was no more effective at preventing oxymorphine induced systolic blood pressure drops than nalorphine.

More extensive studies by Jasinski and Martin[81] compared naloxone to nalorphine, cyclazocine, and placebo. Naloxone had essentially no agonist activity failing to elicit miosis or subjective changes such as drunkiness,

hallucinations, etc. The only characteristic which differentiated naloxone subjects from the placebo control group was more sleepiness. Naloxone effectively antagonized morphine without the development of tolerance to its antagonist actions. It proved to be seven times more potent than nalorphine in precipitating abstinence and differed from the mixed agonist/antagonist agents by failing to show evidence of an abstinence syndrome after the cessation of chronic use.

Although Jasinski's work suggested that naloxone was preferable to cyclazocine or nalorphine as an antagonist agent, larger doses were required for 24 hour blockade making widespread use of this expensive compound for maintenance impractical. A study by Zaks[204] demonstrated that up to 2.4 gm of orally administered naloxone was necessary to ensure 24 hour blockage to a 25 mg dose of heroin while 3 gm was necessary if a heroin challenge was increased to 50 mg. No untoward side effects were noted from these high doses of naloxone and Zaks expressed the need for a longer acting and/or slow release preparation.

Long term outpatient naloxone therapy was studied by Kleber and Pierson.[84,135] The study was conducted over three and one half years with 176 young heroin abusers who were treated in a high intervention setting. This consisted of "confrontation style" therapy with eight hour sessions five days per week. Naloxone was used for the first six months of the year long program at doses of 800 mg per day. The drug was well tolerated and thirty-nine percent of the participants remained opiate free for one to three years after treatment. The 800 mg naloxone dose was less than would be required for 24 hour receptor blockade. However, in this study the eight hours per day of supervision eliminated the need for higher doses.

Naltrexone proved to be one answer to the dosage problem. Studies by Gritz,[57] Martin,[117] Resnick,[148] and Brahen[15] showed that naltrexone's antagonist activity was 17 times more potent than nalorphine and twice as potent as naloxone. Furthermore, naltrexone was 2.5 times more potent than naloxone in its ability to precipitate abstinence having a longer period of actions with a half life which was twice as long as that of naloxone. Oral doses of naltrexone in the 30-50 mg range provided 24 hour blockade to heroin challenges which required up to 3 gm of naloxone. Naltrexone's ability to precipitate morphine abstinence symptoms began within 15-30 minutes and decreased over the next hour. Furthermore, like naloxone, abrupt cessation after chronic use did not produce an abstinence syndrome.

During induction at doses of 20-50 mg, Resnick[148] found that patients complained of nervousness, irritability, difficulty falling asleep, abdominal pain, nausea and vomiting. However, Martin[117] only observed subjective changes in one indivdual who was given an initial dose of 70 mg subcutaneously. Gritz[57] believed that the abdominal complaints may indeed have been from naltrexone since his subjects who had been abstinent for 2.5 months experienced similar symptoms. In any case, these complaints subsided with dosage stabilization indicating that they were only transitory. In a study comparing induction on naltrexone and cyclazocine, Brahen[15] found that naltrexone's gastrointestinal side effects were well tolerated enabling participants to achieve maintenance doses while cyclazocine side effects were too numerous and severe resulting in a high drop out rate.

Changes observed during chronic naltrexone use included a fall in body temperature and an increase in diastolic blood pressure.[57] In all studies, no toxic effects on EKG, blood or urinalysis were noted. As per Resnick,[148] 50 mg

of naltrexone is sufficient for 24 hour blockade of a 25 mg heroin test dose while 48 hour blockade is accomplished with more than 120 mg and 72 hour blockade with 200 mg.

Long term clinical trials have been conducted to assess naltrexone maintenance therapy. Altman, Meyer, Mirin et al.[4] found that naltrexone maintained addicts did not test its antagonist properties. Therefore, extinction could not occur and based on Wikler's theory and these individuals would be susceptible to opiate craving when naltrexone was discontinued. Since their subjects knew that the antagonist was expected to prevent opiate agonist actions, they suggested that the anticipation of successful antagonism might have led to the lack of opiate use. Furthermore, they found that craving levels corresponded to the perceived availability of heroin. The highest craving levels were recorded when heroin was known to be most available.[122] Kleber,[84] on the other hand, has suggested that extinction might be occurring even in the absence of actual drug use. He claimed that abstinence in an environment which was previously associated with drug use could extinguish the drug-seeking response.

In another study, Sideroff[161] followed patients in a nine month outpatient naltrexone program. He found a high drop out rate at one month or less with the rest of the group staying for more than three months. This initial high attrition rate appeared to be due to unacceptable opiate craving leading him to postulate that 3-5 weeks of naltrexone is necessary to achieve a satisfactory reduction in craving. Unlike the Altman, Meyer, Mirin study, his patients did test the naltrexone blockade and found a reduced level of craving afterwards. However, the maximum number of trials for any individual however was two which failed to demonstrate the expected increase frequency of responses prior

to extinction. Patients who left the program later than one month did not complain about craving. Instead they felt uncomfortable in the nonopiate environment or believed that they were ready to be completely free of outside support systems.

In summary, these studies showed that naltrexone may be useful for a small group of well-motivated opiate addicts enabling them to become opiate free without fear of readdiction. Even if extinction is not playing a role antagonists might aid in the protracted abstinence syndrome. As previously discussed, chronic antagonist treatment causes an increase in the number of opiate receptor binding sites. As such, it had been suggested that this receptor enhancement would make patients more sensitive to opiates and decrease the need for both exogenous and endogenous opiates the later of which may be depressed in chronic opiate addiction and contribute to the protracted abstinence syndrome.[155]

USE OF OPIATE ANTAGONISTS FOR DETOXIFICATION

Resnick et al.[149] described a clinical trial in which naloxone precipitated withdrawal was utilized as a method for rapid opiate detoxification. He suggested that a shorter period of detoxification should enable patients to be placed on protective naltrexone therapy sooner and eliminate the vulnerable period of 5-10 opiate free days prior to naltrexone induction. Thirty-three subjects with methadone maintenance doses of 5-20 mg were premedicated with 10-15 mg of diazepam and 0.4 mg of atropine. This was followed by repeated intramuscular injections of naloxone over a one to two day period until precipitated abstinence was eliminated. This procedure was followed by a 1.2

mg naloxone test dose on the second or third day respectively with subsequent induction onto naltrexone therapy. Some of the individuals in the two day detoxification group did have a positive naloxone test and could not be started on naltrexone on that day. Resnick postulated that opiates remaining in the body had reoccupied receptors overnight and that naloxone displacement initiated withdrawal symptoms. He found this procedure to be safe with relatively small changes in vital signs. Most patients in this study preferred a more intense but briefer detoxification to gradual methadone withdrawal.

There has not been much literature on this method of detoxification and a single trial by Riordan (personal communication) proved to be unsuccessful. The patient terminated the trial because of unbearable withdrawal symptoms. As such, Riordan and Kleber[150] attempted an initial clinical trial using naloxone and clonidine in combination. Their study included three heroin abusers with an average habit of 60 mg per day and methadone patient with a 25 mg per day dosage. Opiate was stopped on day one and clonidine was administered in three doses. On day two, intramuscular naloxone doses every two hours starting at 0.2mg and increasing to 0.4 mg were added to the three times per day clonidine regimen as tolerated. This was continued on day three increasing the naloxone dose to 0.8 mg every two hours. On day 4, a naloxone test dose was administered and if no reaction occurred, naltrexone induction was begun. All of the patients were successfully detoxified and had negative naloxone tests on day 4. Withdrawal ratings were highest on day two with scores in the five to nine range after the first two naloxone doses. However, scores for day three showed only one or two symptoms.

Following this initial trial, Riordan and Klebar suggested that naltrexone might be even better than naloxone in this detoxification technique. The

purpose of the current study is to evaluate the effectiveness of a clonidine/naltrexone combination in producing a rapid well tolerated detoxification. The use of naltrexone would permit oral administration and prevent the necessity of frequent intramuscular or intravenous injections.

MATERIALS AND METHODS

This study was divided into two parts comprising a total of five male and three female volunteers who were members in good standing at methadone maintenance programs in Connecticut. Participants were prescreened by both their counselors at their respective methadone clinic and the responsible physician at the Connecticut Mental Health Center in New Haven, Connecticut to determine that detoxification was appropriate. On admission to the locked inpatient ward at Connecticut Mental Health Center, patients were given a standard admission interview with specific emphasis on previous drug abuse history. In addition, they were screened for major illnesses with a thorough physical examination and laboratory work consisting of a CBC with differential, erythrocyte sedimentation rate, electrolytes, blood urea nitrogen, creatinine, glucose, liver function tests, thyroid function tests, VDRL, urinalysis, electrocardiogram, hepatitis titre and where appropriate a pregnancy test. If the subjects had not taken their daily methadone dose this was administered. Baseline measurements were made of vital signs - recording pulse and blood pressure in both the prone and sitting positions. Baseline withdrawal symptomatology was determined by rating for the presence or absence, not degree, of 18 items which included the subjective symptoms: craving, anxiety, goose-flesh, hot and cold flashes, aching of muscles and bones, anorexia, insomnia, restlessness, nausea, vomiting, diarrhea, and spontaneous orgasm as well as the objective items: yawning, perspiration, lacrimation, rhinnorhea, yen sleep, and tremors. Analogue scales were also completed rating energy, nervousness, irritability, feelings of being uninvolved, and unpleasantness on a graded seven point scale. Participants were informed of their right to

discontinue the study at any time. Visitors were not permitted prior to the completion of detoxification but they had unlimited access to the public ward telephone. Subjects were told that they would be undergoing a rapid detoxification using a combination of either methadone, clonidine or placebo and either antagonist or placebo. They would be blind to the types of drugs administered but were guaranteed to be detoxified if they completed the study. Finally, all were given the option of participating in the naltrexone aftercare program.

PART I

Two men and one woman were detoxified on the clonidine/naloxone protocol to demonstrate the efficiacy and safety of this combination as well as determine dosing schedules. The average age of this group was 32$\pm$ 2.5 with an average of 9$\pm$ 4.6 years of opiate addiction and 5.3$\pm$ 3.1 years on methadone maintenance. As a group they had 4.7$\pm$ 4.6 (range 2-10) previous detoxification attempts and had been maintained on an average of 20$\pm$ 0 mg of methadone over the three months prior to admission. On day one, their usual methadone maintenance dose was administered. On day two, the methadone was abruptly stopped and clonidine was administered orally in an orange flavored solution under double blind conditions. Only the physician overseeing the study was aware of dosing schedules. The initial 9AM clonidine dose was 5 µg/kg. Subsequent doses at 3PM and 9PM were individually adjusted on the basis of vital signs and withdrawal symptoms. Withdrawal ratings and analogue scales were completed prior to each dose. Clonidine doses were held for a pulse rate less than 50 or a blood pressure less than 90/60 and the responsible

physician was notified. On day three clonidine was administered every four hours. Two hours after the morning clonidine dose, intravenous naloxone was administered in a single blind fashion. If a test dose of 0.1 mg did not cause severe withdrawal symptoms, it was repeated in one hour. Doses were increased by 0.1 mg every hour as tolerated to maximum of 0.3 mg per dose. Withdrawal ratings and vital signs were measured prior to each naloxone dose and naloxone was held with notification of the responsible physician if symptom ratings exceeded five. Day four continued in the same manner with naloxone doses being increased to a maximum of 0.7 mg per dose. On day five, a naloxone challenge of 1.2 mg IM was administered. At this point, the three subjects were treated differently. One had his clonidine abruptly terminated, another had a rapid dose reduction with a four day taper, and the third had a slow three day taper. Two out of the three subjects expressed an interest in naltrexone maintenance. Induction onto the drug in a nonblind fashion with doses of 5-10 mg every three hours to a maximum of 40 mg on Day 5 was possible if the naloxone challenge test was negative. A single 50 mg naltrexone dose would then be administered starting on day six. Naltrexone was administered orally in fruit juice.

PART II

Three men and two women were studied on a clonidine/naltrexone protocol. The mean age of the group was 28.4$\pm$ 4.0 with an average of 8.6$\pm$ 3.1 years of opiate addiction and 4.4$\pm$ 3.2 years (range 2-10) on methadone maintenance. They had undergone an average of 2.4$\pm$ 0.9 previous detoxification attempts and were admitted on an average three month

methadone maintenance dose of 30.6± 17.4 mg (range 10-58). Days one and two were identical to Part I. On day three they were given clonidine in a double blind fashion and naltrexone in a single blind fashion as described in Part I. Clonidine and naltrexone were administered together at four hour intervals and withdrawal ratings and vital signs were measured prior to each dose. Naltrexone was begun at 1 mg and increased to a maximum of 2 mg per dose as tolerated. (The first subject was actually started at 2 mg but this was abandoned because of the difficulties he encountered - see results). Day four was conducted in the same manner increasing naltrexone to a maximum of 8 mg per dose. On day five, naltrexone was administered at 10 mg per dose until approximately a 40 mg maximum for the day had been reached. In addition, a slow clonidine taper was begun with the aim of tapering the dose by approximately fifty percent per day over a 2-4 day period as tolerated. On day six, naltrexone was given as a single 50 mg dose and on day seven most patients were discharged after a single dose of clonidine and naltrexone. No limit was set on the length of stay and subjects were welcome to extend their stay beyond a week. Flurazepam and chloral hydrate were used as needed for sleep.

Note: Clonidine was suppled as CATAPRES^{R}

Naloxone was supplied as NARCAN^{R}

Naltrexone was supplied by the National Institute on Drug Abuse

RESULTS

PART I - CASE REPORTS

SUBJECT 1 was a 34 year old black male who had a four year history of opiate addiction, a two year history of methadone maintenance, two previous detoxification attempts, and a daily methadone maintenance dose of 20 mg for the three months prior to admission.

DAY 1: On the day of admission he exhibited no withdrawal symptoms.

DAY 2: Clonidine was safely started at a dose of 0.4 mg three times per day. There was no evidence of severe postural hypotension, bradycardia or the emergence of withdrawal symptoms.

DAY 3: He was easily inducted onto naloxone reaching a dose of 0.2 mg per hour by dose four and 0.3 mg per hour by dose eight. Clonidine was increased to 0.45 mg per dose and was effective in minimizing his withdrawal symptoms which averaged 0.9 per rating (range 0-4).

DAY 4: This day proceeded smoothly as well with the subject reaching a naloxone dose of 0.7 mg per hour by dose seven. Clonidine was successfully decreased to 0.4 mg per dose by mid-afternoon and the average number of withdrawal symptoms was lower than on the previous day at 0.6 symptoms per rating.

DAY 5: Clonidine was stopped after an initial 9 AM dose of 0.3 mg. He successfully passed a 1.2 mg naloxone challenge test and was begun on naltrexone induction at 10 mg four times per day. By

the evening, however, his withdrawal symptoms had recurred increasing from a level of one per rating to six per rating. The average number of symptoms for this day was three per rating.

DAY 6: The increase in withdrawal symptoms proved to be only transient. He began a downward trend again with an average of two symptoms per rating. In addition, he was able to take a single 50 mg naltrexone dose without a reemergence of severe abstinence symtoms.

DAY 7: He was discharged after receiving a 50 mg dose of naltrexone. (See TABLE Ia, TABLE Ib and FIGURE 1)

SUBJECT 2 was a 32 year old white male who had a three year history of opiate addiction, an eight year history of methadone maintenance, two previous detoxification attempts, and a methadone maintenance dose of 20 mg for the three months prior to admission.

DAY 1: He exhibited two withdrawal symptoms on admission.

DAY 2: Clonidine was begun at 0.3 mg three times per day. This appeared to be adequate coverage since he only had 1.7 symptoms on average per rating. Although his blood pressure fell from a baseline of 122/90 to 80/50, he did not experience any syncopal episodes and maintained his vital signs at an average blood pressure of 97/62 and a pulse of 81.

DAY 3: He was inducted onto naloxone reaching a dose of 0.2 mg per dose by dose three and 0.3 mg per dose by dose seven. Clonidine was increased to 0.35 mg per dose which successfully minimized his withdrawal symptoms which were on average actually less than on admission at 0.7 symptoms per rating (range 0-3). Vital signs were not

severely affected even at this higher dose of clonidine. On average his blood pressure read 110/73 with a pulse of 71.

DAY 4: He reached 0.4 mg of naloxone by dose three, 0.5 mg by dose five, 0.6 mg by dose ten, and 0.7 mg by dose thirteen. Clonidine was again increased on this day to treat his withdrawal symptoms which had increased to an average of 1.8 symptoms per rating. As on the previous day, vital signs remained stable.

DAY 5: He successfully passed a 1.2 mg naloxone challenge but requested not to be begun on naltrexone induction. In addition, the clonidine dosage was sharply reduced from a total of 2.4 mg (27 µg/kg) on the previous day to 0.4 mg (4 µk/kg). It is important to note that this was a clonidine taper not termination as with Subject 1.

DAY 6: On this day he experienced more withdrawal symptoms averaging 4.3 per rating (range 3-5) while on a clonidine dose of 0.5 mg per day.

DAY 7: An increase in clonidine to 0.7 mg per day was accompanied by a downward trend in his average symptom rating to 3.7.

DAY 8: The downward trend in symptoms continued and he was discharged after final clonidine dose of 0.2 mg and a rating of two on the withdrawal scale. (See TABLE Ia, TABLE Ib, FIGURE 2)

SUBJECT 3 was a 29 year old white female with a ten year history of opiate addiction, a six year history of methadone maintenance, ten previous detoxification attempts, and a daily methadone dose of 20 mg over the three months prior to admission.

DAY 1: She was admitted with a withdrawal symptom rating of one.

DAY 2: Clonidine was ordered at 0.25 mg three times per day and was supplemented with an extra dose of 0.1 mg to cover the increase in withdrawal symptoms which averaged 2.7 per rating. Vital signs remained stable throughout his day without significant drops in blood pressure or pulse changes.

DAY 3: She was slowly inducted onto naloxone and reached 0.2 mg by dose six but did not achieve a dose of 0.3 mg. She appeared to be experiencing more withdrawal symptoms than previous subjects and required a few naloxone doses to be held for symptom ratings of five despite increases in clonidine to 0.4 mg per dose. The average number of symptoms per rating for that day was 3 (range 1-5). The clonidine doses were well tolerated with stable vital signs at an average blood pressure of 100/66 and a pulse of 65.

DAY 4: She was started on 0.3 mg of naloxone reaching 0.4 mg by dose three, 0.5 mg by dose five, and 0.6 mg by dose nine. As during the previous day, the symptom ratings reached a high level. One naloxone dose was cut in half for a symptom rating of seven. However, the usual naloxone dosing regimen was resumed and well tolerated at the next time point. Occasional doses of clonidine in the range of 0.5 mg per dose were required to keep the average symptoms rating low at 3.9 (range 3-7).

DAY 5: A clonidine taper of approximately fifty percent per day was begun. The final total dose of clonidine on this day was 0.8 mg (13 µk/kg) as compared to 2.65 (44 µk/kg) on the previous day. In addition, naltrexone induction was successfully accomplished without a reemergence of withdrawal symptoms.

DAY 6: The clonidine taper was continued and she was given a single 50 mg dose of naltrexone.

DAY 7: This day proceeded as described for day six except that the clonidine was stopped after a final dose of 0.1 mg.

DAY 8: She continued to show a downward trend in the symptom ratings despite the daily 50 mg naltrexone doses and the absence of clonidine therapy. Her average symptom rating for this day was 0.5. Unlike the other subjects she remained for eleven days and actually started on a 150 mg maintenance dose of naltrexone. (See TABLE Ia, TABLE Ib, FIGURE 3)

PART II

SUBJECT 4 was a 23 year old white male who had a five year history of opiate addiction, a three year history of methadone maintenance, two previous detoxification attempts, and a methadone maintenance dose of 30 mg for the three months prior to admission.

DAY 1: He was admitted without any withdrawal symptoms.

DAY 2: Clonidine was successfully administered without evidence of significant blood pressure or pulse changes. He did experience some withdrawal symptoms but these were well managed with an extra dose of clonidine.

DAY 3: Unlike the rest of Group II, he was started on a 2 mg dose of naltrexone. This produced a marked increase in his withdrawal symptoms and one naltrexone dose had to be held while the clonidine was increased to 0.5 mg per dose during the course of the day.

DAY 4: He was able to achieve a dose of 8 mg of natrexone by dose three without an exacerbation of symptoms. In fact, his average withdrawal rating score decreased from 6.5 on day three to 3.7 on this day. Clonidine doses were maintained in the 0.4 - 0.5 range without severe side effects.

DAY 5: A slow clonidine taper was begun while naltrexone doses were increased to 10 mg four times per day.

DAY 6: A single 50 mg dose of naltrexone was well tolerated while the three day clonidine taper continued.

DAY 7: The last dose of 0.2 mg of clonidine was administered and he was discharged without having shown evidence of a reemergence of withdrawal symptoms or evidence of clonidine withdrawal symptomatology. (See TABLE IIa, TABLE IIb, FIGURE 4)

SUBJECTS 5 and 7 will be discussed together because of their similar hospital courses. SUBJECT 5 was a 25 year old Puerto Rican male with an eleven year history of opiate addiction, a two year history of methadone maintenance, three previous detoxification attempts, and a stable methadone maintenance dose of 25 mg per day for at least three months prior to admission. SUBJECT 7 was a 34 year old white female who had a twelve year history of opiate aodiciton, a ten year history of methadone maintenance, one previous detoxification attempt, and an average methadone maintenance dose of 10 mg per day for much greater than three months prior to admission.

DAY 1: SUBJECT 5 was admitted without evidence of any withdrawal symptoms while SUBJECT 7 was rated as having two symptoms.

DAY 2: During clonidine therapy, both subjects experienced a slight increase in their withdrawal symptoms as well as blood pressure drops below 90/60. However, they did not have any syncopal episodes and only experienced lightheadedness on standing. SUBJECT 5 was managed by reducing one of his three clonidine doses by 0.05 mg. SUBJECT 7's dosage was not manipulated in the interest of covering her withdrawal symptoms. This did not appear to be dangerous from a cardiovascular standpoint.

DAY 3: Both subjects were successfully started on naltrexone at 1 mg and achieved a level of 2 mg by the third dose. Increases in withdrawal symptom ratings were treated by increasing the clonidine dose to 0.5 mg in SUBJECT 5. This could not be done for SUBJECT 7 because of borderline blood pressure readings on 0.3 mg of clonidine. When expressed in micrograms per kilogram, SUBJECT 7's clonidine dose was approximately half that for the others in Group II. However, it was not necessary to hold naltrexone doses for either subject since withdrawal symptom ratings were relatively low at 2.3 (range 1-4) for SUBJECT 5 and moderate at 4.6 (range 3-5) for SUBJECT 7 despite her lower levels of clonidine.

DAY 4: Both individuals had achieved an 8 mg dose of naltrexone by dose four. Neither required manipulation of their clonidine doses and both showed evidence of a downward trend in the severity of their withdrawal symptoms.

DAY 5: A clonidine taper was begun and the 10 mg four times per day naltrexone regimen was initiated.

DAY 6: A single 50 mg naltrexone dose was administered while the clonidine taper continued for both subjects. SUBJECT 5 did show a slight increase in symptoms on this day. This may have been due to the fact that he had a more severe clonidine taper on day five as compared to SUBJECT 7. SUBJECT 7 left on the evening of day six without having shown a reemergence of withdrawal symptoms.

DAY 7: The increase in withdrawal symptoms for SUBJECT 5 proved to be transient and the downward trend continued despite the clonidine taper. His last dose of 0.2 mg was given and he was discharged. (See TABLE IIa, TABLE IIb, FIGURES 5,7)

SUBJECT 6 was a 30 year old white female who had a nine year history of opiate addiction, a three year history of methadone maintenance, and three previous detoxification attempts. She was admitted on a dose of 35 mg of methadone but unbeknownst to us had only been on that dose for a week prior to admission. Her highest dose in the three preceding months had been 75 mg with an average dose of 58 mg.

DAY 1: She was admitted with three withdrawal symptoms.

DAY 2: She tolerated the usual clonidine regimen well. In fact, her withdrawal symptoms actually decreased to an average of two per rating.

DAY 3: She was successfully begun on 1 mg of naltrexone and increased to 2 mg by the second dose. Her withdrawal symptoms were kept at an average of 3.3 (range 3-4) with up to 0.5 mg of clonidine.

DAY 4: Clonidine was maintained at 0.45 mg per dose and she reached naltrexone dose of 8 mg by the fourth dose. Her average

withdrawal symptom rating decreased to 2.6 and there was no evidence of adverse effects from clonidine.

DAY 5: A 10 mg per dose naltrexone regimen was begun and a 50 percent clonidine taper was started while the average withdrawal symptomatology remained at 2.6 per rating. In addition, on this day she began complaining about severe anxiety and the feeling that her "insides were going to explode".

DAY 6: The anxiety continued through day 6 despite seven 10 mg doses of diazepam over the preceding 36 hours. When questioned about her thoughts on the matter, it became apparent that she was afraid of being detoxified from methadone and was not sure that she could make it without the drug. In addition, she had multiple family problems which were mounting and not resolvable in the near future. Despite these complications, she was able to take a single 50 mg dose of naltrexone without experiencing a marked rise in her withdrawal symptoms.

DAY 7: Her anxiety level reached a peak on this day and she was given 50 mg of thioridizine which produced a remarkable reduction in her anxiety. At this time the anxiety appeared to be due to outside pressures as opposed to a manifestation of withdrawal. However, her distraught state probably contributed to the upward trend in her withdrawal symptoms on this day.

DAY 8: She received her last dose of clonidine.

DAY 9: She was observed off clonidine while continuing with daily 50 mg naltrexone doses and failed to show a reemergence of withdrawal symptoms. It is of interest that on discharge she was the only member of Group II who elected to try naltrexone maintenance. (See TABLE IIa, TABLE IIb, FIGURE 6)

SUBJECT 8 was a 27 year old white male who had a six year history of opiate addiciton, four year history of methadone maintenance, and three previous detoxification attempts. He also had been detoxifying from higher methadone doses but he had been on a stable dose of 25 mg for three weeks prior to admission. His average methadone dose over the three months prior to admission was 30 mg.

DAY 1: On admission he had no withdrawal symptoms.

DAY 2: This day went well on the usual clonidine regimen.

DAY 3: Naltrexone was begun at 1 mg. However, he was unable to advance to 2 mg because of severe anxiety and tension. These were felt to be withdrawal symptoms since he reported similar reactions during previous detoxification attempts. Furthermore, these symptoms were not present prior to the onset of naltrexone therapy. His average symptom rating remained at 4.2 (range 1-6) despite doses of clonidine of up to 0.5 mg. When the anxiety was not relieved by 10 mg of diazepam and 2 gm of chloral hydrate, 100 mg of thioridizine was tried. This proved to be beneficial and repetition was not necessary.

DAY 4: He was able to advance to 7 mg of naltrexone by dose four while on 0.6 mg of clonidine per dose. This seemingly high dose of clonidine was well tolerated and he maintained an average blood pressure of 99/70 with a pulse of 74. This is not surprising when the dose is evaluated in terms of micrograms per kilogram. His total clonidine dose on that day was actually not much greater than the other members of the group. In addition, his symptoms decreased ot an average of 1.2 per rating (range 0-3).

DAY 5: As with the other members of Group II, he was able to reach the 10 mg Q.I.D. naltrexone dosage regimen on day five as well as begin the clonidine taper.

DAY 6: He tolerated the 50 mg naltrexone dose and was able to continue the clonidine taper despite a small increase in withdrawal symptoms for 1.2 on day four to 2.7 on day six.

DAY 7: The downward trend on symptoms resumed and he was discharged after a final clonidine dose of 0.1 mg. (See TABLE IIa, TABLE IIb, FIGURE 8)

GROUP II - COMBINED DATA

On the whole, Group II tolerated this protocol very well. Although lightheadedness on standing was experienced by most subjects, there were no synocopal episodes and all marked drops in blood pressure could be handled satisfactorily by individual dose manipulations. Average sitting blood pressure and pulse readings for the group are charted in Table IV and graphed in Figure 10.

The group showed a peak clonidine dose on DAY 3 of 2.9± 0.68 mg (44± 9.2 µg/kg) and were able to complete a three to four day clonidine taper without significant reemergence of withdrawal symptoms or evidence of a clonidine withdrawal syndrome (Table III). Withdrawal symptoms generally appeared within 45 minutes of naltrexone administration and abated over the next two hours.

A peak in withdrawal symptoms was seen on DAY 3. This was the time at which naltrexone therapy was initiated. After this day, there was a downward

trend in the average number of withdrawal symptoms with a plateau of approximately two symptoms per rating between DAYS 5 and 7 (see Figure 9). The most common symptoms were insomnia, restlessness, muscle and bone aching, anxiety, craving, hot and cold flashes, anorexia, gooseflesh, diarrhea and yawning. A few subjects experienced tremors, yen sleep, rhinnorhea, lacrimation and nausea. No one reported vomiting, spontaneous orgasm or perspiration. Most of these symptoms had abated by DAY 6 and on DAY 7 the only symptoms reported were anxiety, bone and muscle aching, insomnia, restlessness, and rhinorrhea. Of these only insomnia and bone and muscle aching were reported more than 50% of the time. (See Table V).

The means of Group II's analogue scales show that energy reached a low during DAYS 3 and 4 and returned to baseline by the end of the study. Most appeared to be nervous on DAY 1 but gave lower ratings as the study progressed and as they became more comfortable with the staff and the environment. Scales of irritability, uninvolved and unpleasantness increased over the days of maximal withdrawal symptoms and decreased toward baseline at the end of the study. (Figures 11-15).

Reasons for desiring detoxification at this time included feelings of being well established in a job and family situations; wishing to make a break from the drug environment which included methadone maintenance clinics; and pressure from family members. All subjects reported satisfaction with this method of detoxification. Many related that their symptoms were less severe than during previous detoxification attempts. Although one subject felt that his symptoms on DAY 3 were comparable to previous experiences, the fact that they only lasted for one to two days made this method more desirable for him.

Only one subject wished to participate in the naltrexone program. The other subjects felt that they needed to make a complete break from any association with the drug culture and were confident of their ability to do so without structured pharmacological or social support systems.

DISCUSSION

Many theories have been invoked to explain the events which occur during opiate dependence, withdrawal and relapse. They have included possible changes in opiate receptor number and/or affinity; changes in postsynaptic β receptor number, reduced levels of endogenous opiate peptides secondary to either decreased synthesis or increased enzymatic degradation; and hyperactivity of central noradrenergic neurons. Specific attention to this last hypothesis arose with the discovery of a relationship between the locus coeruleus and cortical norepinephrine turnover.[92,93] LC firing was observed to increase during naloxone induced withdrawal in morphine dependent rats[2] and norepinephrine turnover was increased in LC innervated brain regions during naloxone precipitated withdrawal.[27,102] The LC could be depressed by morphine, met-enkephalin, and clonidine - an α2 adrenergic agonist.[94,202,99,11,2] Furthermore, clonidine depressed the elevated levels of norepinephrine turnover during withdrawal.[27] Behavioral studies in nonhuman primates showed that similar behaviors could be induced by LC stimulation, piperoxane administration, human threats, and opiate withdrawal[43,140,141,144,145] while clonidine, morphine and met-enkephalin were able to depress the LC stimulation and piperoxane induced behaviors.[43,71,142] Finally, clonidine was observed to suppress the opiate withdrawal syndrome in rats.[38]

These studies led to the hypothesis of a hyperadrenergic state during withdrawal centered in the LC which could be suppressed by the nonopiate drug clonidine. Clinical trials in opiate addicts proved to be successful and were

repeated by several investigators.[22,44,45,46,50,49,184,188,190] However, this method required 8-14 days and did not eliminate the vulnerable period of five to ten days after methadone is stopped before it is possible to initiate antagonist aftercare therapy. Prior to the clonidine studies, trials were conducted with naloxone in an attempt to find a more rapid method of detoxification which would shorten the lag period.[149] Although this was reported to be successful, other investigators were not able to repeat the results. Recently, Riordan and Kleber[150] attempted to use clonidine and naloxone in combination. Their success with an initial trial prompted this study to confirm the efficacy and safety of the method, determine appropriate dosing schedules, and attempt substitution of the longer acting orally effective antagonist naltrexone in the place of naloxone.

The results of PART I demonstrated that a safe rapid three day detoxification from methadone could be accomplished as previously described by Riordan and Kleber using a clonidine/naloxone combination. There were no severe changes in blood pressure or pulse which could not be controlled by minor individual clonidine dose manipulation. All subjects could begin induction onto naltrexone on the fourth day after methadone was abruptly stopped. Furthermore, 24 hour receptor coverage at a dose of 50 mg of naltrexone could be achieved by the fifth day. The various schedules used to taper clonidine demonstrated that a slow three to four day taper was necessary to prevent the reemergence of withdrawal symptoms. Using such a method also prevented the appearance of a clonidine withdrawal syndrome. Based on these results, it seems doubtful that naloxone detoxification accompanied only by premedication with atropine and diazepam would be tolerated in a rapid detoxification as described by Resnick.[149] Certainly, SUBJECT 3 was unable to advance as

quickly in the naloxone induction protocol as compared to other subjects despite fairly high doses of clonidine.

The results of PART II indicated that the same three day detoxification could be accomplished using the longer acting orally active opiate antagonist naltrexone in combination with clonidine. Therefore, the necessity of frequent intravenous or intramuscular injections both in this study and others [149,150] could be eliminated. Naltrexone's longer half life and greater potency in precipitating abstinence did not become a problem since a slow induction with one mg increments was possible and all the abstinence symptoms with the exception of anxiety in SUBJECT 8 could be controlled with clonidine. The importance of starting at one mg was illustrated in SUBJECT 4 who experienced severe symptoms when begun at two mg and required a naltrexone dose to be held. The significance of the anxiety reaction in SUBJECT 8, which appeared to be related to precipitated abstinence and required the use of additional medication i.e. diazepam and thioridizine, cannot be evaluated without examining a larger population. As previously discussed, the anxiety in SUBJECT 6 did not appear to be part of the withdrawal syndrome and no other subjects in either the naloxone or naltrexone protocols had similar experiences. In any case, the single dose of thioridizine was effective in SUBJECT 8 and did not require repetition. He was able to continue on with the protocol as originally designed and complete it in the same amount of time as the rest of the group.

As described in the clonidine/naloxone study and numerous inpatient and outpatient clonidine detoxification studies, there were no irreversible adverse effects from clonidine. Individualized dosing regimens proved to be effective in controlling both abstinence symptoms and vital sign stability. The necessity of

such individual attention was well illustrated by the fact that SUBJECT 8 could tolerate 0.6 mg of clonidine per dose while SUBJECT 7 was unable to be increased above 0.3 mg on DAY 3 without compromising her cardiovascular status.

All subjects experienced most of their abstinence symptoms during the first three days of detoxification, were able to begin on 10 mg per dose of naltrexone on the fifth day after methadone withdrawal, and tolerated a single 50 mg dose of naltrexone on the sixth post methadone day. The slight increase in withdrawal symptom on DAYS 5 and 6 in some subjects was not severe. Both the clonidine taper and 50 mg naltrexone coverage could be continued. This increase may have represented a need for more clonidine on DAY 5 because of residual withdrawal symptoms. Unlike the heroin abstinence syndrome which peaks at two to three days and lasts for five to ten days, the methadone withdrawal syndrome peaks at three to four days and lasts for two to three weeks. This extended period of time could explain the upward trend in symptoms seen on days five and six in subjects who had a more rapid clonidine taper. A larger dose of clonidine with a slower taper probably would have prevented this from occurring. It is of note that subject four had the least amount of dosage reduction between days five and six and did not show this upward trend in withdrawal symptoms. If the patients had been detoxified from heroin, there might have been a more intense withdrawal syndrome initially. However, the increase in withdrawal symptoms during the clonidine taper probably would not have occurred since withdrawal would have been virtually complete at that time.

There was no apparent correlation between the initial methadone maintenance dose and the severity of the withdrawal syndrome with this

method. All subjects regardless of being on low dose (10 mg) or higher dose (35 mg) methadone therapy were able to ultimately complete the protocol as designed. Reactions appeared to be very individualized as SUBJECT 7 who was on 10 mg for many months actually experienced more withdrawal symptoms than SUBJECT 5 who was on 25 mg per day for several months. Previous studies by Gold[49] had demonstrated that clonidine detoxification could be applied to people with a 15 mg requirement as well as 75 mg.

The types of symptoms experienced by the subjects were similar to those described by Charney[22] in a study on 22 patients in an inpatient detoxification trial on clonidine alone. As in that study, restlessness, anxiety, insomnia, and muscle and bone aching were very prominent. The presence of hot and cold flashes, craving, goose-flesh, anorexia, diarrhea, yawning, tremors, yen sleep, rhinnorhea, lacrimation, and nausea represented symptoms up to grade three and would be expected in the first few days of rapidly induced withdrawal with the antagonist. The symptoms remaining on DAYS 6 and 7, i.e., anxiety, insomnia, anorexia, and diarrhea could represent those observed during the first week of naltrexone therapy in other groups.[57,148] However, they could also be withdrawal symptoms as previously discussed.

Comparison of the clonidine/antagonist method of detoxification ot other methods reveals that this method which can be completed in approximately a week. This is considerably shorter than either methadone taper which required a minimum of three weeks in most studies[87,138,201]; abrupt cessation of methadone which is followed by at least three weeks of symptoms[88,116]; or clonidine detoxification which requires 8-14 days after abrupt termination of methadone. Using data supplied by Charney (see Tables III and VI), on ten patients who were begun on clonidine and treated as needed to minimize

withdrawal symptoms, it is apparent that although larger doses of clonidine were necessary on DAYS 3 and 4 for the group treated with naltrexone, the group as a whole was able to achieve lower mean clonidine doses sooner. In the clonidine/naltrexone study, the average dose on DAY 6 was 0.66 $\pm$ 0.25 mg while the clonidine group required 1.1 $\pm$ 0.3 mg. Furthermore on DAY 7, the clonidine naltrexone subjects had been tapered to 0.25 $\pm$ 0.17 mg while the clonidine patients needed 1.0 $\pm$ 0.3 mg to suppress their abstinence symptoms. Presumably, this represents the more rapid detoxification induced by antagonist therapy. The antagonist precipitates withdrawal by displacing opiates from their receptors. In doing so, it disrupts the equillibrium between the drug and its receptor. This might cause the methadone to be more rapidly metabolized than usual and create a shorter withdrawal syndrome.

IMPLICATIONS

From this pilot study, it appears that the clonidine/antagonist methods could be applied to the methadone patient population in the following manner. Methadone could be stopped at a level of approximately 20 mg and clonidine started on an outpatient basis. The next three days beginning with naltrexone induction would need to be conducted as an inpatient. This is necessary to monitor the hypotensive actions of clonidine and individual reactions to naltrexone induction. Furthermore, there would be benefit from the close one to one interactions available in the inpatient setting. Dishcarge would occur when the 50 mg dose of naltrexone was reached and the clonidine taper could be continued as an outpatient. In this way the patient would be on 24 hour naltrexone coverage and less susceptible to relapse in the community.

Certainly this method of detoxification is not appropriate for all opiate addicts. Prospective participants should be well screened to determine reasons for detoxification as well as emotional and social stability. This point was well illustrated by the problems encountered with SUBJECT 6. The findings of Cushman[29] and Valliant[186] should be kept in mind paying special attention to employment history and the degree of involvement in the drug-free environment. This method of detoxification would be especially appropriate for the client electing naltrexone aftercare since it would eliminate the five to ten day period post-detoxification previously required prior to the initation of antagonist therapy.

FUTURE RESEARCH WITH POSSIBLE IMPROVEMENT

More definite conclusions with statistical analysis could be drawn if a larger patient population was studied. Specific attention could be paid to the problem of anxiety as well as the effects of initial methadone maintenance dosage on outcome. The use of double blind methods for both medications and their administration in identical solutions would be preferable. The use of thioridizine, diazepam and flurazepam could certainly be criticized. In the cases of diazepam and flurazepam, these drugs have been shown to depress LC firing.[55] In this respect, they would add to the effects of clonidine. Insomnia and anxiety are problems which might affect successful outcome in this study. The use of these agents could just as well be viewed as an application of the same principles which led to the initial trials with clonidine. Certainly, one must keep in mind the fact that clonidine itself has been reported to cause insomnia and anxiety in individuals not undergoing withdrawal. Finally, it would be helpful to follow these individuals for at least a week and preferably longer

post-detoxification to monitor for the reemergence of withdrawal symptoms and/or relapse.

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APPENDIX

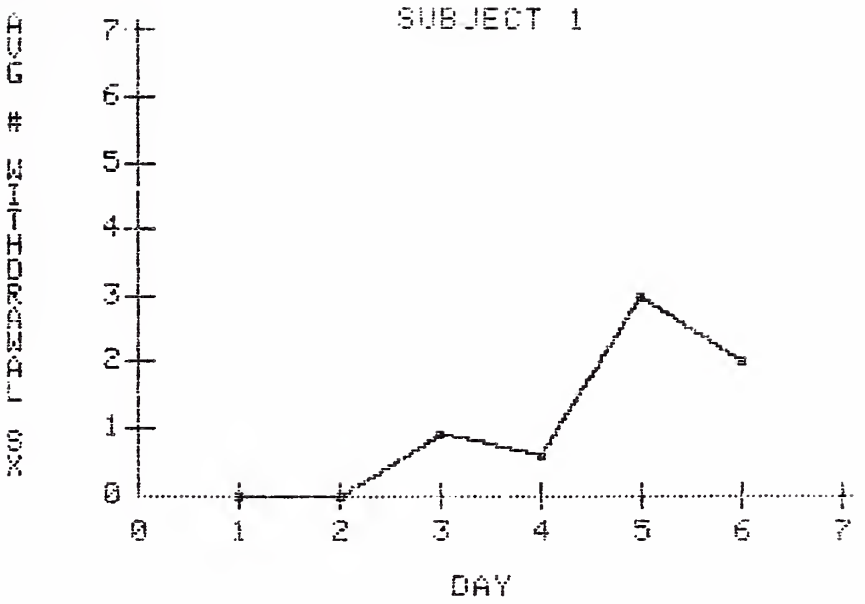

FIGURE 1. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

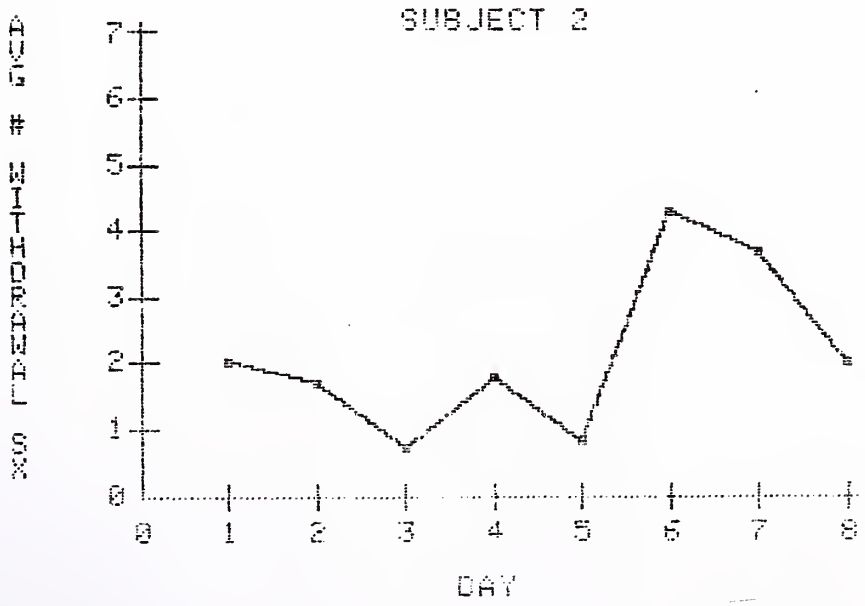

FIGURE 2. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

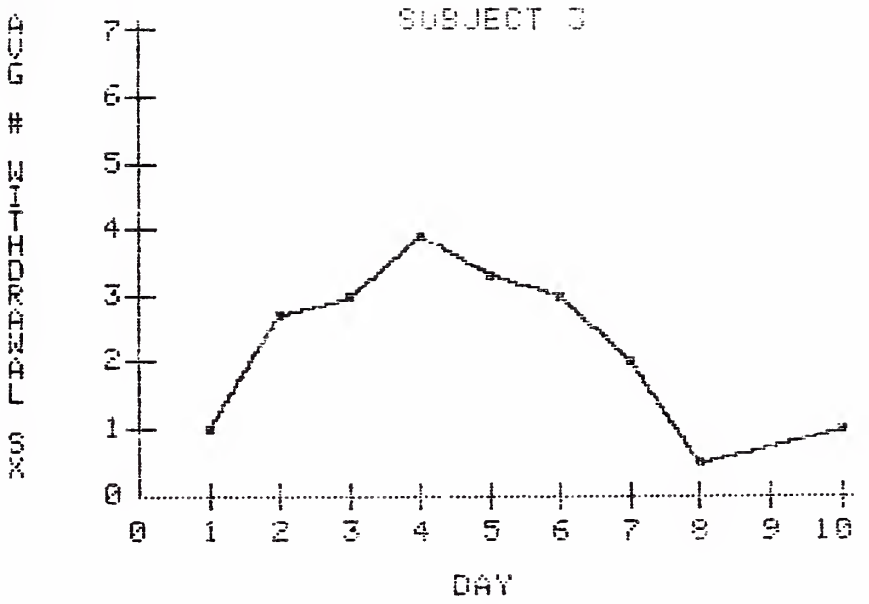

FIGURE 3. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

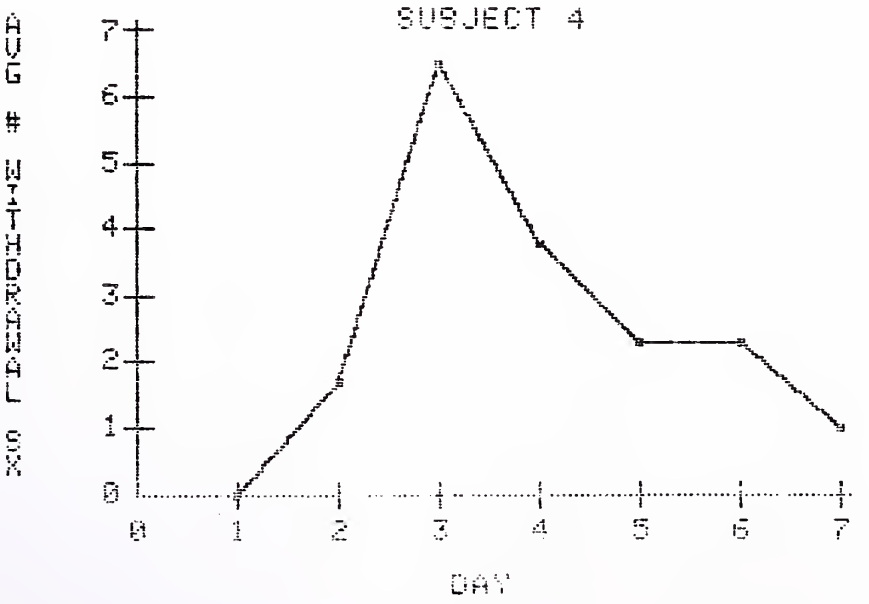

FIGURE 4. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

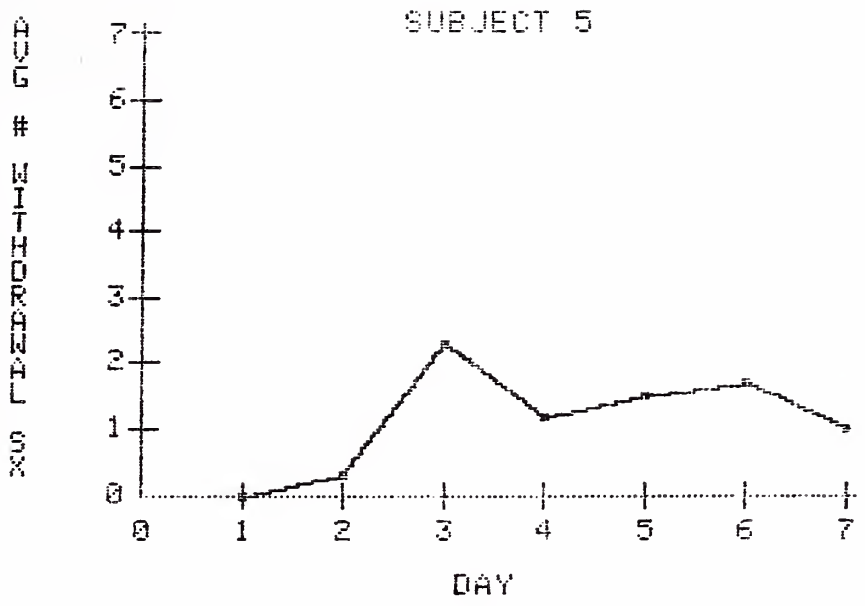

FIGURE 5. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

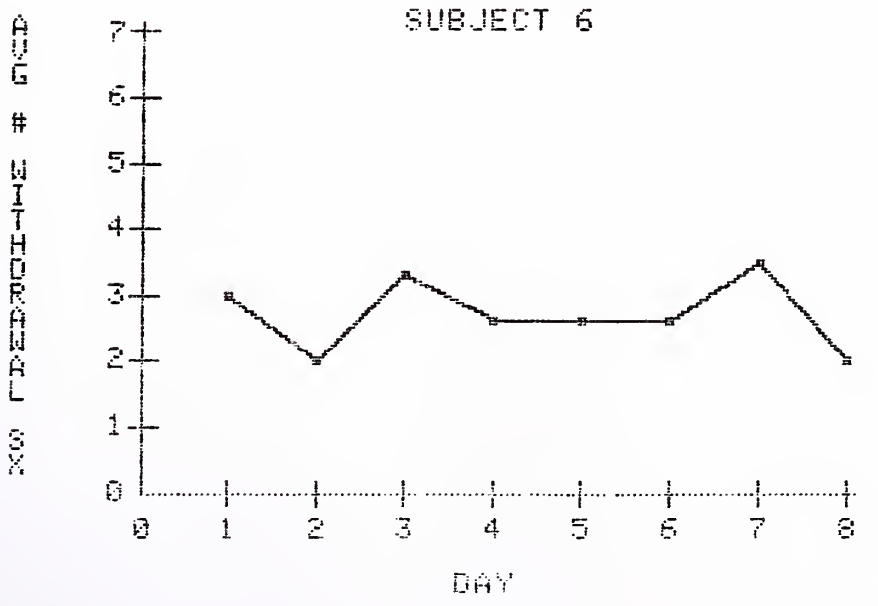

FIGURE 6. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

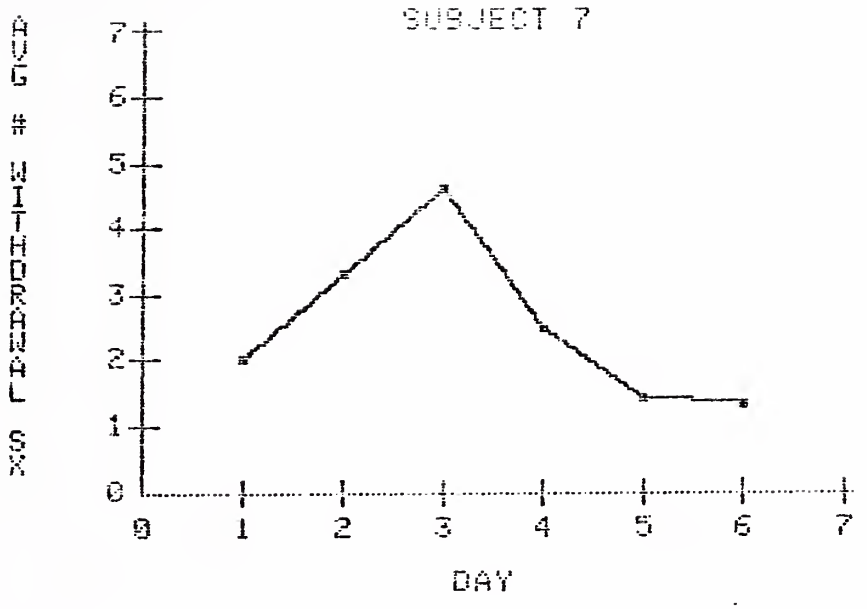

FIGURE 7. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

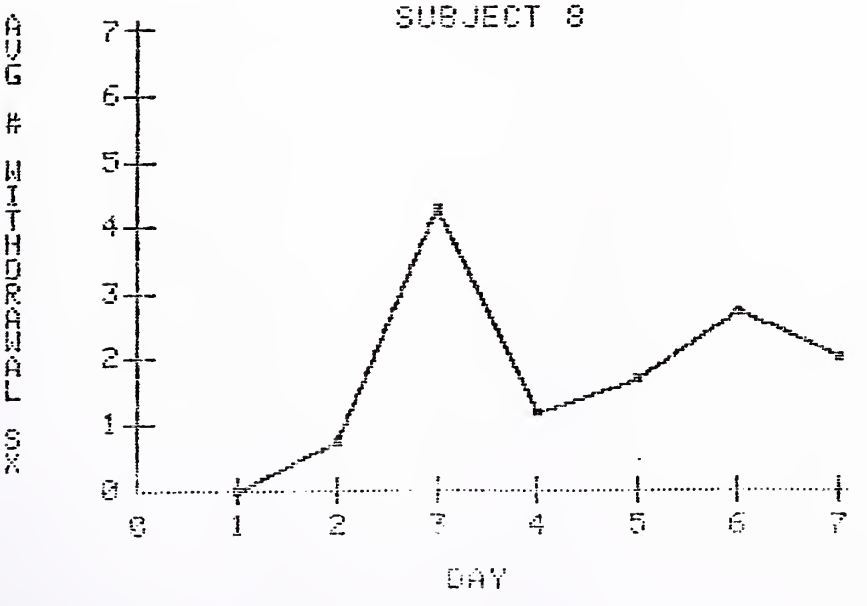

FIGURE 8. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY

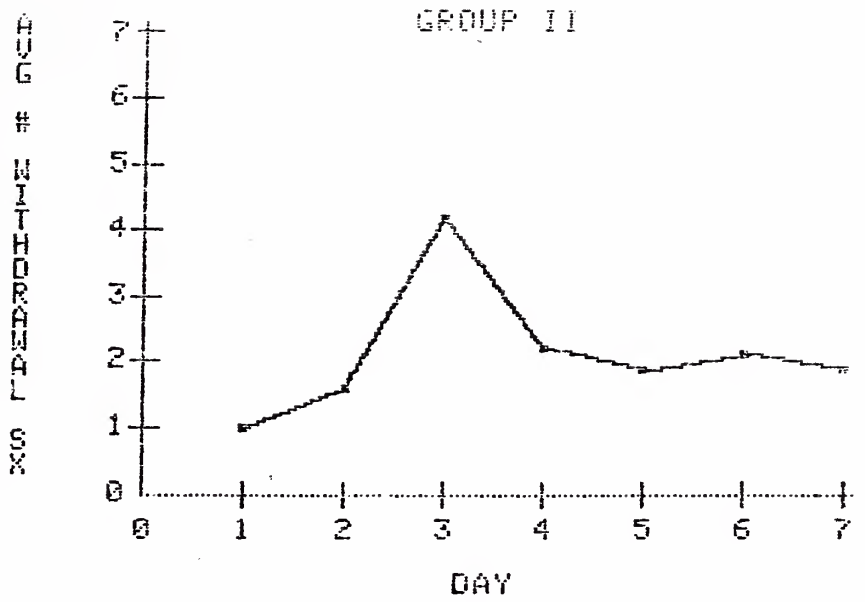

FIGURE 9. AVERAGE NUMBER OF WITHDRAWAL SYMPTOMS VS. DAY-GROUP II

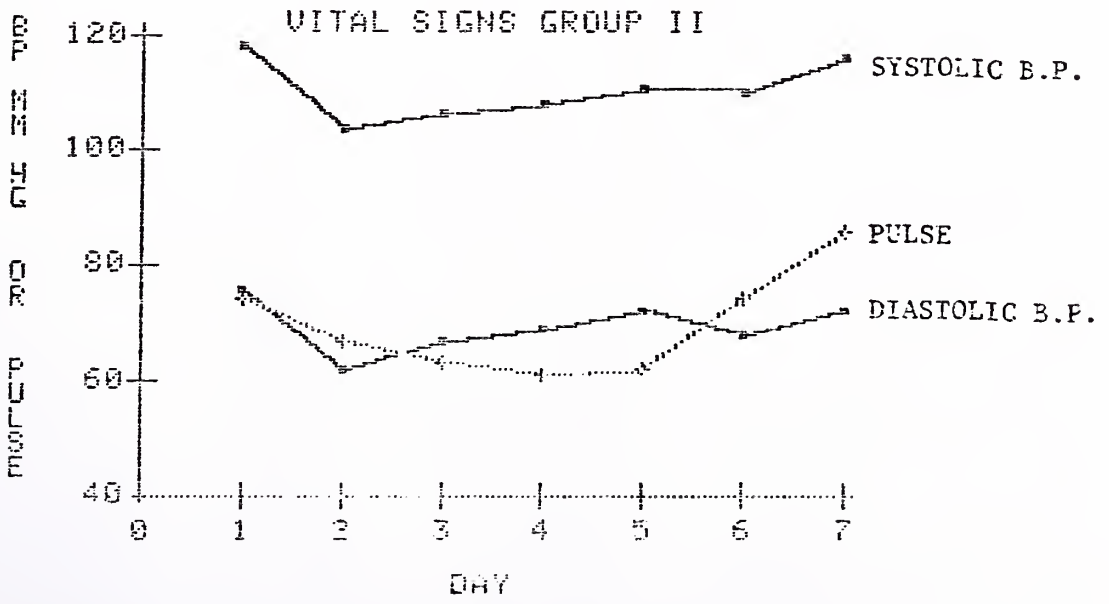

FIGURE 10. AVERAGE SITTING BLOOD PRESSURE AND PULSE- GROUP II

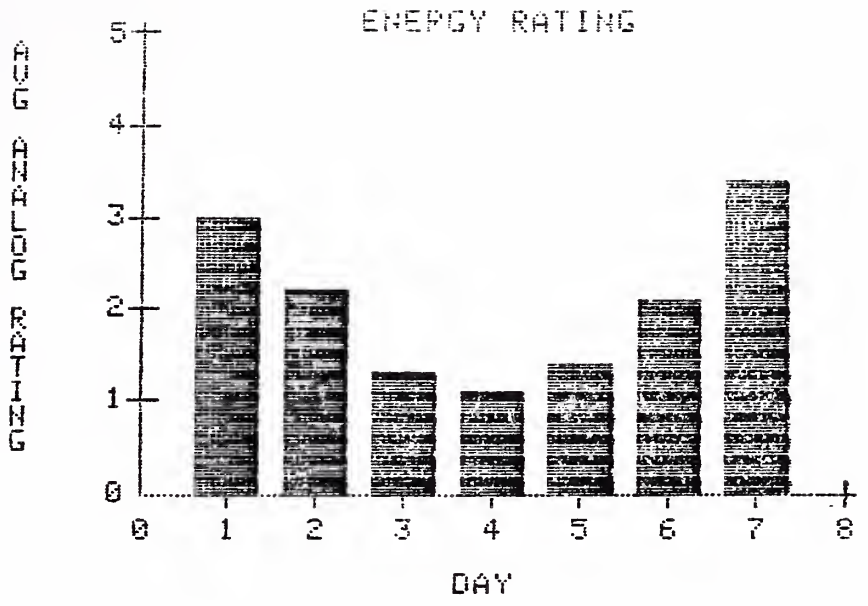

FIGURE 11. AVERAGE ENERGY RATING VS. DAY- GROUP II

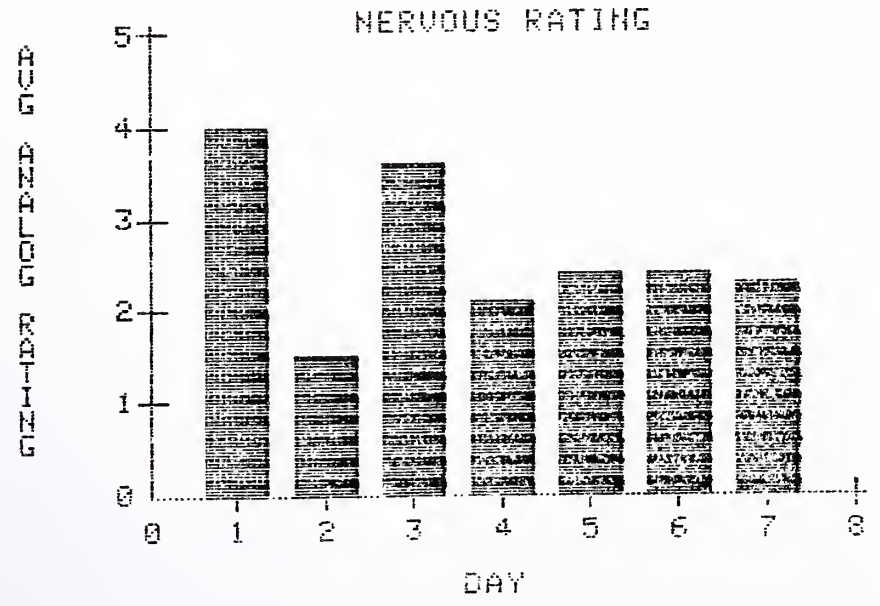

FIGURE 12. AVERAGE NERVOUS RATING VS. DAY- GROUP II

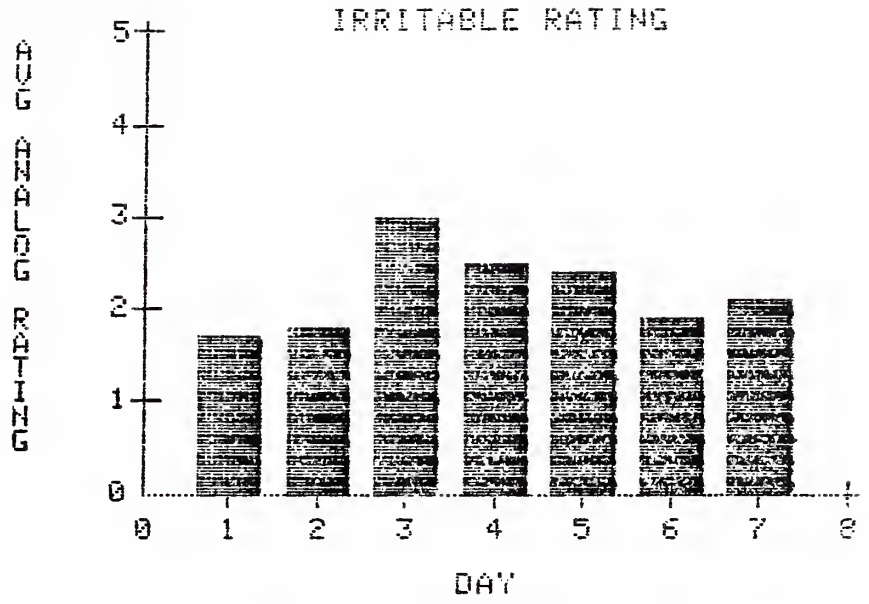

FIGURE 13. AVERAGE IRRITABLE RATING VS. DAY- GROUP II

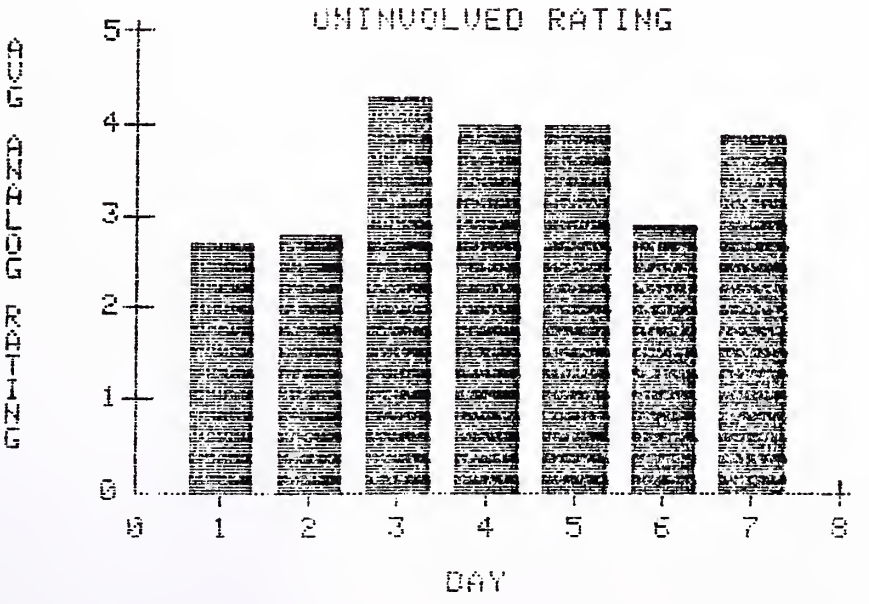

FIGURE 14. AVERAGE UNINVOLVED RATING VS. DAY- GROUP II

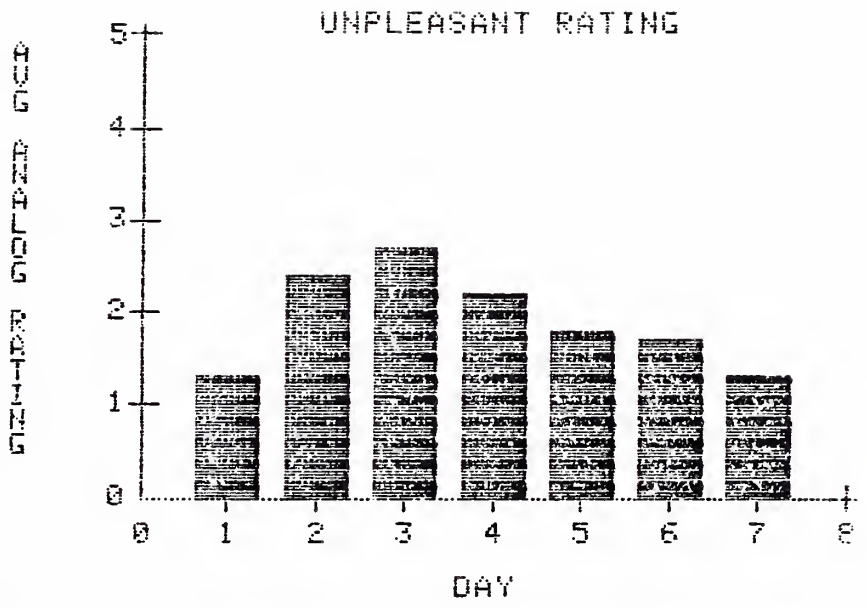

FIGURE 15. AVERAGE UNPLEASANT RATING VS. DAY- GROUP II

TABLE Ia-DRUG DOSAGES-GROUP I

DAY	1	2	3	4	5	6	7	8	9	10	11
DRUG / SUBJECT	METHADONE	CLONIDINE	CL/NL*	CL/NL	CL/NL/NT*	CL/NT*	CL/NT	CL/NT	NT	NT	NT
1	20 MG	18	38/82	36/229	4/18/588	0/735	0/735	-	-	-	-
2	20 MG	10	24/58	27/142	4/21/0	6/0	8/0	2/0	-	-	-
3	20 MG	14	36/60	44/202	13/0/667	5/833	2/833	0/833	833	833	2500

*CL=clonidine; NL=naloxone; NT=naltrexone;CL/NL=clonidine/naloxone; CL/NL/NT=clonidine/naloxone/naltrexone; CL/NT=clonidine/naltrexone; All clonidine, naloxone, and naltrexone doses are expressed in units of μg/KG/DAY.

TABLE Ib- DRUG DOSES-GROUP II

DAY	1	2	3	4	5	6	7	8	9
DRUG / SUBJECT	METHADONE	CLONIDINE	CL/NT*	CL/NT	CL/NT	CL/NT	CL/NT	CL/NT	NT
4	30 MG	21	52/156	41/531	14/625	13/781	3/781	-	-
5	25 MG	18	47/193	42/789	12/702	9/877	4/877	-	-
6	35 MG	15	47/162	40/544	20/706	13/735	7/735	3/735	735
7	10 MG	14	28/203	28/656	11/625	5/781	-	-	-
8	25 MG	12	45/91	45/403	16/584	10/649	1/649	-	-

* CL=clonidine; NT=naltrexone; CL/NT=clonidine/naltrexone; All clonidine and naltrexone doses are expressed in units of μg/KG/DAY.

TABLE IIa- DRUG DOSAGES IN MG/DAY- GROUP 1

DAY	1	2	3	4	5	6	7	8	9	10	11
DRUG / SUBJECT	METHADONE	CLONIDINE	CL/NL*	CL/NL	CL/NL/NT*	CL/NT*	CL/NT	CL/NT	NT	NT	NT
1	20	1.20	2.6/5.6	2.45/15.6	0.3/1.2/40	0/50	0/50	-	-	-	-
2	20	0.90	2.1/5.2	2.4/12.6	0.4/1.9/0	0.5/0	0.7/0	0.2/0	-	-	-
3	20	0.85	2.25/3.6	2.65/12.1	0.8/0/40	0.3/50	0.1/50	0/50	50	50	150

*CL=clonidine; NL=naloxone; NT=naltrexone; CL/NL=clonidine/naloxone; CL/NL/NT=clonidine/naloxone/naltrexone; CL/NT=clonidine/naltrexone.

TABLE IIb- DRUG DOSES IN MG/DAY- GROUP II

DAY	1	2	3	4	5	6	7	8	9
DRUG / SUBJECT	METHADONE	CLONIDINE	CL/NT*	CL/NT	CL/NT	CL/NT	CL/NT	CL/NT	NT
4	30	1.35	3.3/10	2.6/34	0.9/40	0.8/50	0.2/50	-	-
5	25	1.0	2.7/11	2.4/45	0.7/40	0.5/50	0.2/50	-	-
6	35	1.05	3.2/11	2.7/37	1.35/48	0.9/50	0.5/50	0.2/50	0/50
7	10	0.9	1.8/13	1.8/42	0.7/40	0.3/50	-	-	-
8	25	0.9	3.5/7	3.5/31	1.2/45	0.8/50	0.1/50	-	-

*CL=clonidine; NT=naltrexone; CL/NT=clonidine/naltrexone

TABLE III- AVERAGE DAILY DRUG DOSES- GROUP II DAYS 1-7

DAY / DRUG DOSAGE	1	2	3	4	5	6	7
METHADONE MG/DAY	25±9.4	-	-	-	-	-	-
CLONIDINE MG/DAY	-	1.04±0.19	2.90±0.68	2.60±0.61	0.97±0.29	0.66±0.25	0.25±0.17
CLONIDINE μg/KG/DAY	-	16±3.5	44±9.2	39±6.5	15±3.6	10±3.3	4 ±2.5
NALTREXONE MG/DAY	-	-	10.4± 2.2	37.8±5.7	42.6±3.7	50.0± 0	50.0± 0
NALTREXONE μg/KG/DAY	-	-	161±44	585±145	648±54	765±83	760±95

TABLE IV- AVERAGE SITTING BLOOD PRESSURE, PULSE, AND WITHDRAWAL SYMPTOMS- GROUP II

DAY / PARAMETER	1	2	3	4	5	6	7
SYSTOLIC BLOOD PRESSURE MM HG	117±14.3	96±11.2	100±9.3	102±10.5	106±6.7	105±9.6	114±12.7
DIASTOLIC BLOOD PRESSURE MM HG	76±10.3	62±8.4	67±8.0	69±9.8	72±6.2	68±6.1	72±9.8
PULSE BEATS/MIN.	74±7.9	67±19.1	63±9.5	61±11.8	62±14.5	74±20.1	86±12.1
WITHDRAWAL SYMPTOMS	1.0±1.4	1.6±1.2	4.2±1.6	2.2±1.1	1.9±0.5	2.1 ±0.6	1.9±1.2

TABLE V- AVERAGE FREQUENCY OF WITHDRAWAL SYMPTOMS- GROUP II

SYMPTOM \ DAY	1	2	3	4	5	6	7
CRAVING	0	0	0.30	0.05	0.05	0	0
ANXIETY	0.20	0.07	0.61	0.16	0.28	0.27	0.13
GOOSEFLESH	0.20	0.33	0.35	0.20	0.10	0.20	0
HOT AND COLD FLASHES	0	0.07	0.42	0.22	0	0	0
BONE, MUSCLE ACHING	0	0.13	0.52	0.47	0.31	0.73	0.50
ANOREXIA	0.20	0.27	0.49	0.40	0.37	0.23	0
INSOMNIA	0	0	0.60	0.60	0	0.20	0.60
RESTLESSNESS	0	0.27	0.43	0.16	0.32	0	0.25
NAUSEA	0	0	0.06	0	0	0	0
VOMITING	0	0	0	0	0	0	0
DIARRHEA	0	0	0.22	0.11	0.19	0.33	0
SPONTANEOUS ORGASM	0	0	0	0	0	0	0
YAWNING	0	0.33	0.17	0	0.20	0.33	0
PERSPIRATION	0	0	0	0	0	0	0
LACRIMATION	0	0.17	0.13	0.08	0.04	0	0
RHINORRHEA	0.20	0.13	0.09	0.09	0.05	0	0.20
YEN SLEEP	0	0.07	0.11	0.03	0.10	0	0
TREMORS	0	0	0.02	0	0	0	0
AVERAGE NUMBER OF RATINGS*	1	3	7	6	4	3	1

*More ratings were obtained on various days because the status of the patient was changing more rapidly.

TABLE VI- AVERAGE CLONIDINE DOSE/DAY FOR TEN PATIENTS TREATED WITH CLONIDINE ALONE FOR METHADONE DETOXIFICATION *

DAY	DRUG DOSE MG/DAY
1	METHADONE-23 MG
	CLONIDINE
2	1.0 ± 0.2
3	1.0 ± 0.2
4	1.0 ± 0.2
5	1.1 ± 0.3
6	1.1 ± 0.3
7	1.0 ± 0.3
8	1.0 ± 0.3
9	0.8 ± 0.3
10	0.6 + 0.3
11	0.3 ± 0.1
12	0

* SOURCE: D. Charney-personal communication

LEGENDS

FIGURES 1-8 - Average number of withdrawal symptoms vs. day for subjects 1-8.

FIGURE 9 - Average number of withdrawal symptoms vs. day for Group II.

FIGURE 10 - Average sitting systolic blood pressure, diastolic blood pressure, and pulse vs. day for Group II.

FIGURES 11-15 - Average analogue scale rating for the variables of energy, irritable, uninvolved, nervous, and unpleasant vs. day for Group II. The average number of ratings used to generate this data was one for DAY 1; three for DAY 2; seven for DAY 3; six for DAY 4; four for DAY 5; three for DAY 6; and one for DAY 7. There were more ratings on days in which there were frequent changes in the status of the patient.

TABLE Ia - Doses of methadone, clonidine, naloxone, and naltrexone vs. day for subjects 1-3. Methadone is expressed in units of mg/day while clonidine, naloxone, and naltrexone are expressed in units of µg/kg/day. A dash in the box refers to the fact that the subject was not present on that day. In all cases the subject had been discharged.

TABLE Ib - Same as TABLE Ia except that it is doses of methadone, clonidine, and naltrexone for subjects 4-8.

TABLE IIa - Doses of methadone, clonidine, naloxone, and naltrexone vs. day for subjects 1-3. All drug doses are expressed in units of mg/day.

TABLE IIb - Same as TABLE IIa except that it is doses of methadone, clonidine, and naltrexone for subjects 4-8.

TABLE III - Average daily doses of methadone, clonidine, and naltrexone for Group II (subjects 4-8). Methadone is expressed in units of mg/day while clonidine and naltrexone are expressed in both units of mg/day and µg/kg/day.

TABLE IV - Average sitting systolic blood pressure, diastolic blood pressure, and pulse as well as the average number of withdrawal symptoms vs. day for Group II.

TABLE V - Average frequency of individual withdrawal symptoms vs. day for Group II. The frequency was calculated by dividing the number of times a symptom was reported in a day by the number of ratings taken during that day. More ratings were obtained on various days because the status of the subject was changing more rapidly.

TABLE VI - Average clonidine dose per day for ten patients treated with clonidine alone as a method of methadone detoxification. The average methadone maintenance dose is also indicated for DAY 1. Both methadone and clonidine are expressed in units of mg/day. Data was supplied by D. Charney, MD.

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